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BACTERIOLOGY AND SEVERE COMPLICATIONS OF OTITIS MEDIA

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Academic Dissertation

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To my Family

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ABSTRACT

Background: The bacteriology, the clinical picture and the treatment of otitis media (OM) have changed over the last decades. New bacterial species, like *Alloiococcus otitidis*, are suggested to be associated with OM and severe complications of OM are encountered only rarely.

Methods: 118 children with acute otitis media (AOM) and 123 children with otitis media with effusion (OME) were included in two separate bacteriological studies using bacterial culture and polymerase chain reaction (PCR). In the two retrospective studies focusing on the complications of OM, all the adult [older than 15 years (N=30)] and pediatric [15 years and younger (N=33)] patients treated for intratemporal (ITC) or intracranial complications (ICC) of OM over the past 10 years (1990-2000) at the Department of Otorhinolaryngology in the Helsinki University Central Hospital were included.

Results: *A. otitidis* was not detected by culture. PCR detected DNA of *A. otitidis* in 25% (30/118) of the middle ear effusion (MEE) samples in AOM. The clinical outcome of the *A. otitidis* positive children compared with the *A. otitidis* negative children did not differ in AOM. In OME, 20% (25/123) of the MEE samples were positive for *A. otitidis* by PCR. *A. otitidis* positivity in PCR correlated significantly with the long persistence and the mucoid appearance of MEE.
The annual age-adjusted incidence of acute intratemporal (ITC) and intracranial (ICC) complications in children and adults was 1.1/100 000 and 0.3/100 000, respectively. Among the children an ITC was found in 97% (32/33), and ICC in 3% (1/33). Among the adults, 73% (22/30) had an ITC and 27% (8/30) had an ICC. *Streptococcus pneumoniae* (8/33) and *Pseudomonas aeruginosa* (7/33) were the bacteria most frequently found in the MEE and mastoid effusions of the children with ITC and ICC. Among the adults, *S. pneumoniae* (5/30) and *Streptococcus pyogenes* (5/30) were the bacteria most often cultured. The signs of abscess forming ITC or ICC were associated with performed mastoidectomy among both the pediatric and adult patients. All children recovered completely. Among the adults, the complication of OM caused permanent hearing loss in 30% (9/30) of the patients. One adult died from otogenic meningitis.

Conclusions: Our results suggest that *A. otitidis* has no clinical significance in AOM. In OME, the existence of *A. otitidis* DNA correlates with the persistence of MEE. Severe complications of OM are rare today. Among children these complications are usually intratemporal and present with AOM, but among adults ICC and COM and cholesteatoma behind the complication should be suspected more easily. In adults the clinical picture of ITC and ICC of OM is often slowly progressing and mild. Antibiotics are the basis of the treatment and surgery should be considered in abscess-forming ITC and ICC of OM.

ABBREVIATIONS

AM	acute mastoiditis
AOM	acute otitis media
COM	chronic otitis media
CRP	C-reactive protein
CT	computed tomography
DNA	deoxyribonucleic acid
ICC	intracranial complication
ITC	intratemporal complication
ME	mastoid effusion
MEE	middle ear effusion
MRI	magnetic resonance imaging
OM	otitis media
OME	otitis media with effusion
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PTA	pure tone average
RAOM	recurrent acute otitis media
RNA	ribonucleic acid
TM	tympanic membrane
URI	upper respiratory tract infection

ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I Leskinen K, Hendolin P, Virolainen- Julkunen A, Ylikoski J, Jero J. *Alloiococcus otitidis* in acute otitis media. Int J Pediatr Otorhinolaryngol 2004; 68(1): 51-56.

II Leskinen K, Hendolin P, Virolainen-Julkunen A, Ylikoski J, Jero J. The clinical role of *Alloiococcus otitidis* in otitis media with effusion. Int J Pediatr Otorhinolaryngol 2002; 66: 41-48.

III Leskinen K, Jero J. Intratemporal and –cranial complications of acute otitis media in children in southern Finland. Int J Pediatr Otorhinolaryngol 2004; 68: 317-24.

IV Leskinen K, Jero J. Acute complications of otitis media in adults over the past ten years in the Helsinki hospital district. Submitted

V Leskinen K, Jero J. Acute mastoiditis caused by *Moraxella catarrhalis*. Int J Pediatr Otorhinolaryngol 2003; 67: 31-33.

1 INTRODUCTION

Bacterial infection is considered the main etiological factor of acute otitis media (AOM) and acute complications of different types of otitis media (OM) (Bluestone and Klein 2001). Our knowledge about the bacteriology of OM has changed markedly during the last 100 years (Valentine 1924, Nielsen 1945, Kilpi et al. 2001), and, at the same time, there has been a big change in the clinical presentation and treatment of OM in developed countries (Kafka 1935, Lahikainen 1953, Juselius and Kaltiokallio 1972, Palva et al. 1985). Some of the bacterial species that caused middle ear infections in the first half of the 20th century are cultured today only rarely from the middle ear effusions (MEE) in AOM (Valentine 1924, Kilpi et al. 2001). On the other hand, some of the bacteria that were earlier considered harmless are now on the list of the most commonly found pathogenic bacteria in AOM (Jero et al. 1997, Kilpi et al. 2001). The availability of penicillin and other antibiotics since the 1950s divides the century into a pre-antibiotic and antibiotic era, the two periods with completely different problems with respect to the treatment of OM (Lahikainen 1953, Juselius and Kaltiokallio 1972).

During the last decades the most feared purulent OM complications are encountered only rarely, and the incidence of chronic OM complications has been low (Palva et al. 1985). As a result, clinical experience with the diagnosis and treatment of these complications has decreased. The use of antibiotics modifies the clinical picture of OM and sometimes masks the progression of infection leading to latent complications (Faye-Lund 1989). The worldwide increasing bacterial resistance to the antibiotics used to treat OM points to the importance of an accurate clinical and bacteriological diagnosis of these infections.

The traditional bacterial diagnosis of OM is based on the bacterial culture of MEE or mastoid effusion (ME). With respect to AOM the bacterial culture of MEE is still the gold standard for identifying the possible bacterial etiology of infection (Bluestone and Klein 2001). Today myringotomy is performed only on patients with prolonged or otherwise complicated OM. Many of these patients have been treated with antibiotics before the MEE sample has been obtained. In OM with effusion (OME) the bacterial culture of MEE is more often negative (Sipilä et al. 1981, Jero et al. 1996) suggesting low or no bacterial activity in the middle ear. The detection of bacterial deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) could offer a new method for the bacterial detection in OM (Post et al. 1995, Hendolin et al. 1999).

2 REVIEW OF THE LITERATURE

2.1 Acute otitis media

2.1.1 Definition

The definition of AOM has been discussed over the years. The Research Conference in Fort Lauderdale 1983 (Paparella et al. 1985) started the development work that has provided guidelines for the currently used definition.

AOM is an acute infection of the middle ear cavity. The onset of signs and symptoms is rapid. For the diagnosis of AOM, there must be both acute ear-related local or systemic symptoms and signs of MEE. Acute discharge through a tympanic membrane perforation or through a tympanostomy tube with signs of acute infection is also considered AOM (Karma et al. 1987, Rosenfeld and Bluestone 1999, Bluestone and Klein 2001). The definition of recurrent AOM (RAOM) has varied (Klein 1984, Alho et al. 1990). Many studies use the criterion of 3 AOM episodes in 6 months or 4 episodes in 1 year (Klein 1984, Paradise 2002).

2.1.2 Epidemiology

The incidence of AOM is strongly age-related, and AOM is one of the most common reasons for antibiotic therapy in children (Paradise et al. 1997). It is estimated that 500 000 cases of AOM are diagnosed annually in Finland (Niemelä et al. 1999). The peak incidence of AOM occurs during the second half of the first year of life. Thereafter the incidence of AOM gradually decreases (Sipilä et al. 1987, Teele et al. 1989, Alho et al. 1991). During the first year of life, 42-62% of children experience at least one episode of AOM (Teele et al. 1989, Alho et al. 1991). By 2 years of age, up to 71% of Finnish children have had at least one episode of AOM (Alho et al. 1991). The incidence of AOM has increased during the last few decades in Finland (Joki-Erkkilä et al. 1998).

2.1.3 Pathogenesis

The etiology of AOM is multifactorial including anatomical, infectious, immunological, genetic, allergic, environmental and social factors (Casselbrant et al. 2004, Bluestone and Klein 2001). Dysfunction of the eustachian tube and impairment in the ventilation and clearance of the middle ear are probably the most important factors contributing to the development of AOM (Stenfors et al. 1985, Casselbrant et al. 1988, Buchman et al. 1995). The eustachian tube of infants is more susceptible to functional disturbances than the eustachian tube of older children and adults (Bylander 1980, Sadler-Kimes et al. 1989). This is one of the factors explaining the decreasing incidence of AOM with increasing age (Stenström et al. 1991).

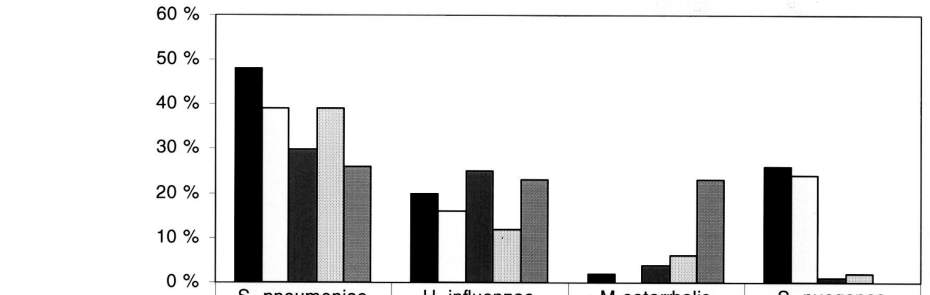
An upper respiratory tract infection (URI) usually starts the process leading to AOM and symptoms of a URI are associated with AOM in 94% of cases (Arola et al. 1990). Many recent

studies have shown the important role of viruses in the development of AOM, although the exact mechanisms behind their action are still unclear (Arola et al. 1990, Arruda et al. 1997, Pitkäranta et al. 1998, Winther et al. 2002). Viruses, as a sole pathogen, are found in 5% of MEE of AOM by culture and antigen detection methods (Chonmaitree et al. 1986, Heikkinen et al. 1999). Viral RNA is detected in 33-41% of MEE of AOM by PCR in Finland (Nokso-Koivisto et al. 2004). Viral infections induce mucosal swelling in the nasopharynx and eustachian tube leading to an impaired ventilation and clearance of secretions from the middle ear (Buchman et al. 1995, Bluestone 1996). This results in a negative pressure and collection of effusion in the middle ear. Viral infections also enhance bacterial colonization and adherence in the nasopharynx (Wadowsky et al. 1995, Hament et al. 1999, Tong et al. 2000). It is suggested, that the nasopharyngeal bacteria then ascend via the eustachian tube into the middle ear to cause the acute middle ear infection (Bluestone and Klein 2001). In addition, viruses and bacteria together induce an increased production of inflammatory mediators in the middle ear and they are probably responsible for the clinical signs and symptoms of AOM (Chonmaitree et al. 1996). Combined viral and bacterial infection of the middle ear has also been shown to lead to a decrease in the antibiotic concentrations in the middle ear (Jossart et al. 1994, Canafax et al. 1998).

2.1.4 Bacteriology

Bacteria are considered to be the major etiological factor of AOM. The bacterial etiology of AOM has been studied with the use of MEE cultures and, during the last decade, with PCR. Bacteria have been cultured in 67-84% of MEE samples of AOM (Luotonen et al. 1981, Bluestone et al. 1992, Kilpi et al. 2001). The three bacteria most frequently found in MEE samples of AOM are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (Karma et al. 1987, Bluestone et al. 1992, Kilpi et al. 2001). Less frequently found bacteria are *Streptococcus pyogenes*, *Staphylococcus aureus*, *Chlamydia trachomatis*, coagulase-negative staphylococci, and diphteroids (Chang et al. 1982, Bluestone et al. 1992, Virolainen et al. 1994, Kilpi et al. 2001). The changing bacteriology of AOM is presented in Figure 1. *H. influenzae* is isolated significantly less often from MEE of AOM in children over 3 years of age than in children under 3 years of age (Luotonen et al. 1981). Otherwise, the bacteriology of AOM seems to be almost similar in different age groups (Schwarz and Rodriguez 1981, Celin et al. 1991, Kilpi et al. 2001, Turner et al. 2002), as well as in different geographic areas of developed countries (Bluestone et al. 1992, Leibovitz et al. 1998, Commisso et al. 2000, Kilpi et al. 2001).

Figure 1. Changing bacterial etiology of AOM.



	S. pneumoniae	H. influenzae	M.catarrhalis	S. pyogenes
Nielsen 1945	48 %	20 %	2 %	26 %
Lahikainen 1953	39 %	16 %	0 %	24 %
Nilson et al. 1969	30 %	25 %	4 %	1 %
Luotonen et al. 1981	39 %	12 %	6 %	2 %
Kilpi et al. 2001	26 %	23 %	23 %	0 %

Since the introduction of antibiotics, *S. pneumoniae* has been the bacteria most frequently found in MEE samples of AOM. Today *S. pneumoniae* is found in 18-26% of MEE specimens of AOM in Finland (Virolainen et al. 1994, Kilpi et al. 2001), and in 16-50% in other countries (Paraskaki et al. 1995, Hoberman et al. 1996, Arguedas et al. 1998, Sih 2001). Although more than 80 different serotypes of *S. pneumoniae* exist, only some of them are markedly associated with AOM. The most frequently found serotypes are 19, 23, 6, 14 and 11 accounting for 78% of all AOM caused by *S. pneumoniae* (Karma et al. 1987, Kilpi et al. 2001). The rapidly increased antibiotic resistance of *S. pneumoniae* has increased the interest to this bacterium. In Finland, 4-6% of *S. pneumoniae* strains are penicillin resistant (Manninen et al. 1997, Kilpi et al. 2001). However, in the United States, the proportion of strains not susceptible to penicillin ranges between 15% and 62% (Jacobs et al. 1999). In addition, the macrolide resistance of *S. pneumoniae* is also increasing (Mason et al. 2003, Reinert et al. 2003). In Finland, 11% of *S. pneumoniae* were resistant to erythromycin in year 2000 compared with 5.3% in 1997 (Pihlajamäki et al. 2002). In the United States, the proportion of macrolide resistant *S. pneumoniae* is 20-30% (Jacobs and Johnson 2003).

H. influenzae was first mentioned as an AOM pathogen in 1928 (Wirth 1928). Primarily because of the difficulties to detect *H. influenzae* in culture, it was not until 1945 that this bacterium was more commonly accepted as an etiologic factor in AOM (Nielsen 1945). In those earlier days, *H. influenzae* was found in 16% of the AOM effusions studied in Finland

(Lahikainen 1953). In current studies the corresponding incidence has ranged from 16% to 23% (Jero et al. 1996, Kaijalainen et al. 2000) and has been shown to be 7-40% in other countries (Bluestone et al. 1992, Gehanno et al. 2001, Sih 2001). Today, almost all *H. influenzae* positive cases of AOM are caused by nontypable strains. In a recent study in Finland, 14% of the *H. influenzae* strains causing AOM produced beta-lactamase (Kilpi et al. 2001).

During the last 20 years, the proportion of *M. catarrhalis* (former *Branhamella catarrhalis*) positive effusions in AOM has increased markedly. Before the 1980s, *M. catarrhalis* was generally considered an innocent and nonpathogenic bacterium. In 1981 serologic evidence of the pathogenic role of *M. catarrhalis* in AOM was introduced (Leinonen et al. 1981). Then in 1983 two different groups reported a significant increase in the incidence of *M. catarrhalis* in the MEE of pediatric patients with AOM in the United States (Kovatch et al.1983, Shurin et al. 1983). In the study of Shurin et al. (1983), the incidence of *M. catarrhalis* increased from 6% to 27% between 1979 and 1982. Recent studies have shown geographic differences in the incidence (1-23%) of *M. catarrhalis* in AOM (Commisso et al. 2000, Gehanno et al. 2001, Sih 2001, Kilpi et al. 2001). Low incidence of *M. catarrhalis* in AOM has been reported from Brazil and Argentina (Sih 2001, Commisso et al. 2000). In Finland, *M. catarrhalis* has been cultured in 9-23% of the MEE specimens of AOM (Jero et al. 1996, Kilpi et al. 2001). Today over 90% of the *M. catarrhalis* strains isolated from MEE specimens of AOM produce beta-lactamase (Kilpi et al. 2001).

In the pre-antibiotic era *S. pyogenes* was the bacterium most frequently found in MEE specimens of AOM, especially in cases with scarlatina or acute tonsillitis (Valentine 1924, Nielsen 1945). However, the use of penicillin in the treatment of these diseases has decreased the incidence of *S. pyogenes*, and today it is found only rarely in the MEE of AOM (Jero et al. 1997, Kilpi et al. 2001). *S. aureus* is an uncommon cause of AOM, and it is found in less than 5% of MEE samples in AOM (Bluestone et al. 1992, Jero et al. 1997). Low numbers of coagulase-negative staphylococci and diphtheroids are found in AOM, but their role is uncertain and they are often considered to be nonpathogenic commensals or contaminants from the ear canal (Bluestone and Klein 2001). *Alloiococcus otitidis* is a Gram-positive coccus found in MEE samples of OME (Faden and Dryja 1989). It is suggested that it might be a potential middle ear pathogen in OME (Faden and Dryja 1989, Bosley et al. 1995). However, there are no reports of *A. otitidis* in AOM.

In studies of AOM there is always a significant number of culture-negative MEE specimens. In recent studies in Finland, it has been 17-22% (Virolainen et al. 1994, Kilpi et al. 2001). However, the finding that culture negative MEE specimens of AOM contain polymorphonuclear leukocytes or pneumococcal antigens and antibodies suggests a bacterial cause also in these episodes (Karma et al. 1987, Broides et al. 2002). Many different factors can be related

to culture-negative MEE specimens in AOM. The microbial etiology can be nonbacterial, or the bacteria can be fastidious and difficult to culture. Antibiotic treatment prior to the sample collection and the possible presence of antimicrobial enzymes or immunoglobulins in MEE may suppress the growth of bacteria (Bluestone and Klein 2001).

PCR identification of bacteria in OM is based on the amplification and detection of bacterial DNA from MEE (Mullis and Faloona 1987, Saiki et al. 1988). In PCR, a double-stranded DNA is first denatured by heat, and, when the temperature is lowered, the primers anneal to the separated strands at the boundaries of the target region. Then DNA polymerase enzyme extends the primer-template complex to produce new complementary strands. When these steps are repeated, the target DNA sequence is amplified exponentially. The amplification product is then detected, for example, by agarose gel electrophoresis or Southern blotting.

PCR is an extremely sensitive method for detecting bacterial DNA. PCR has been used widely for the detection of bacteria in MEEs. However, controversy exists about the clinical relevance of detecting bacterial DNA in MEE. It has been proposed that bacterial DNA in MEE could be a remnant of a previously cleared infection (Cantekin 1996) rather than an indication of viable bacteria in the MEE. Peizhong et al. (2000) showed that MEE is able to inhibit DNA nuclease and the normal breakdown of bacterial DNA in MEE. They concluded that DNA detected by PCR might represent a remnant of non-viable bacteria rather than ongoing infection. However, it has been shown in the chinchilla model of OM that bacterial DNA from non-viable bacteria does not remain amplifiable in MEE longer than a day (Post et al. 1996, Aul et al.1998). Later, it was shown that the majority (81.5%) of MEE samples that contained endotoxin were positive for the gram-negative bacteria *H. influenzae* and *M.catarrhalis* by PCR (Dingman et al. 1998). The authors concluded that the source of endotoxin is viable, but nonculturable bacteria present in the MEE. Rayner et al. (1998) detected, in addition to *H. influenzae* genomic DNA, messenger ribonucleic acid (mRNA) of the constitutive gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Messenger RNA has a short half-life, and it would confirm the presence of viable bacteria in MEE. Of 93 MEE samples of OME, only 11 (11.3%) were positive by culture, whereas 29 (31.5%) tested positive for genomic DNA. All of these PCR-positive samples were also positive for mRNA, an indication of bacterial metabolic activity for *H. influenzae*. Palmu et al. (2004) studied 2595 MEE samples of AOM by PCR and compared the results with the results of pneumococcal culture. PCR was positive for 1222 (47.1%) of the MEE samples. In bacterial culture, 709 (27.3%) of the MEE samples were positive for *S. pneumoniae*. A culture-negative and PCR-positive MEE was often related to a clinically milder infection, compared with *S. pneumoniae* culture-positive AOM. A positive PCR seemed to indicate the presence of viable, but non-culturable *S. pneumoniae* in MEE.

The sensitivity and specificity of PCR to indicate pneumococcal involvement in MEE of AOM has varied. Virolainen et al. (1994) studied 180 MEE samples of AOM and compared the results of bacterial culture with those of pneumolysin-specific PCR for *S. pneumoniae*. In culture *S. pneumoniae* was found in 33 (18%) samples, but with PCR it was detected in 51 (28%) MEE samples. However, three of the *S. pneumoniae* culture-positive MEE samples were negative for PCR. Saukkoriipi et al. (2002) used a real-time quantitative PCR to detect *S. pneumoniae* in 50 MEE specimens from children with AOM. Real-time PCR was positive in 26 samples, whereas only 17 samples yielded positive result by culture. The sensitivity and specificity of real-time PCR, when compared with culture were 100% and 73%, respectively.

2.1.5 Clinical picture and diagnosis

The clinical picture of AOM varies. Most patients with AOM have viral URI, and many of the acute symptoms of AOM are the same as those of viral URI (e.g., rhinitis, cough, fever, gastrointestinal symptoms, loss of apetite, irritability or restless sleep). Fever as a single symptom is found in 23-60% of children with AOM and in 28-77% of children with URI without AOM (Schwartz et al. 1981, Niemelä et al. 1994, Heikkinen and Ruuskanen 1995, Kontiokari et al. 1998). Ninety percent of children with AOM have a fever or an earache, whereas 72% of the children with URI without AOM have these same symptoms (Niemelä et al. 1994).

Earache and other ear-related symptoms (rubbing or pulling the ear, feeling of ear-block) are the most common complaints of children with AOM, and at least one of these is found in 59-78% of children with AOM (Niemelä et al. 1994, Heikkinen and Ruuskanen 1995, Kontiokari et al.1998). Children younger than 2 years often cannot express their ear symptoms, and the only symptoms indicating AOM may be irritability and restlessness. Ear pulling is a common sign in infants, but without concomitant URI it does not indicate AOM (Baker 1992). In the study of Niemelä et al. (1994) two-thirds of the children under 2 years of age had AOM-associated ear-related symptoms. However, if restlessness, irritability and ear symptoms all are included, these symptoms are found in 83% of children (Hayden and Schwartz 1985). It should also be remembered that earache does not always indicate a middle ear problem. Other possible sources of ear pain are lesions in the nerve supply area of the trigeminal, facial, glossopharyngeal, vagus, great auricular or lesser occipital nerve (e.g., tonsillitis, pharyngitis or external otitis) (Bluestone and Klein 2001). On the other hand, about one-third of the children under 2 years of age with AOM have no ear-related symptoms (Niemelä et al. 1994).

Hearing loss, tinnitus and vertigo are also possible signs of AOM. Older children are capable of verbalizing the loss of hearing, but, with younger children, the loss of function is often expressed by parents as a suspicion of hearing loss. Vertigo and tinnitus are sometimes associated with AOM, and they are usually due

to eustachian tube dysfunction. However, vertigo can also be associated with nystagmus and be a sign of complicated AOM with labyrinthitis (Bluestone and Klein 2001).

In physical examination the possible conditions predisposing to OM should be noted. Genetic and developmental disturbances, such as the Treacher Collins syndrome and Down syndrome, are associated with an increased incidence of middle ear infections. Cleft palate with its variations and bifid uvula also involve an increased risk of OM (Stool and Randall 1967, Paradise et al. 1969, Taylor 1972). Nasal and nasopharyngeal pathology (e.g., sinonasal infections, polyposis and tumors) should be excluded (Bluestone and Klein 2001).

Because there is no single symptom or combination of symptoms specific for AOM, its diagnosis can only be verified by the detection of MEE. The examination of the auricle, the periauricular area and the external auditory canal is important for differential diagnostic purposes and for the recognition of possible complications of OM. Pneumatic otoscopy is used to examine the appearance, position, and mobility of the TM. The most reliable signs of AOM with respect to the TM are cloudiness or a yellow color, a bulging position, and impaired mobility (Karma et al. 1989, Arola et al. 1990). A common finding for the TM is redness, but it is found in less than half of the children with AOM (Arola et al. 1990). Thus, redness of the TM as a single finding does not confirm the diagnosis of AOM (Karma et al. 1989). It should also be remembered that a small proportion (1-5%) of children with AOM have a TM that is normal in color or mobility (Karma et al. 1989). Otoscopy is also a very subjective examination. Its accuracy is highly dependent on the observer´s experience. Correctly performed pneumatic otoscopy is a reliably diagnostic tool (Karma et al. 1989, Jones and Kaleida 2003). Still, tympanocentesis (needle aspiration of MEE) or myringotomy (incision of the TM) are the only direct methods with which the presence of MEE can be verified. One of these should be used when a bacterial diagnosis of MEE is needed or there are signs of complications of AOM (Bluestone and Klein 2001). However, myringotomy does not seem to improve the recovery from AOM (Puhakka et al. 1999).

All the aforementioned clinical signs and symptoms of AOM are subjective, and therefore, the risk of a false diagnosis always exists. Tympanometry is an objective diagnostic tool for measuring middle ear pressure, the presence of MEE, and TM mobility. The result of tympanometry is highly dependent on the patient´s cooperation. With cooperative patients its specificity is over 90%, and its sensitivity is about 80% (Koivunen et al. 1997). However, with non-cooperative patients the sensitivity falls to 71% and the specificity to 38%. In addition, with non-cooperative patients, tympanometry is often technically impossible to perform adequately (Koivunen et al. 1997, Palmu et al. 1999). Nevertheless, when these limitations are kept in mind, tympanometry is a useful aid in the diagnosis of AOM. Acoustic reflectometry offers an alternative way to study the presence of MEE objectively. It was introduced in 1984 (Teele and Teele 1984). The

main advantage of acoustic reflectometry, when compared with tympanometry, is that an air-proof ear seal for pressurization is not required, and it is less technique-dependent than tympanometry. Therefore, the measurement can be done even when the cooperation of the patient is not optimal. The sensitivity and specificity of acoustic reflectometry and tympanometry seem to be almost the same (Block et al. 1998). Acoustic reflectometry has also proved to indicate MEE in AOM accurately (Block et al. 1999), but the diagnosis of AOM always demands both a clinical picture of AOM and the detection of MEE.

2.1.6 Treatment

Today the treatment of AOM in Finland is based on the use of antibiotics and symptom-reliving medication. Because, in 69-86% of cases (Mygind et al. 1981, Burke et al. 1991), AOM resolves spontaneously, watchful waiting is an alternative to antibiotics. In Finland, tympanocentesis, myringotomy, and surgical treatment are used in complicated cases or when the microbial etiology of AOM should be confirmed (Puhakka et al. 1999).

In pre-antibiotic era, waiting and myringotomy were the only treatment options for AOM. The introduction of sulfonamides in the 1930s and penicillin in the 1940s radically changed the clinical picture of AOM. The report of Lahikainen (1953) shows the dramatic effect of antibiotics on the outcome of AOM. In a material of 629 patients, 176 were given penicillin and 453 were treated without antibiotics. In the group treated with antibiotic, there were no complications of AOM. In contrast, in the group treated without antibiotics, the following intratemporal (ITC) or intracranial (ICC) complications occured: 7 cases of mastoiditis, 1 case of meningitis and 1 fatal case of sinus thrombosis with an associated brain abscess. The morbidity and mortality associated with AOM has been shown to decline significantly and the recovery from AOM is shorter when accurate antibiotic treatment is used (Nielsen 1945, Lahikainen 1953, Rudberg 1954, Tarkkanen and Kohonen 1970). In addition, complicated AOM cases in association with *S. pyogenes* positive tonsillitis and scarlatina have almost disappeared. These tremendous results have justified the use of antibiotics for AOM.

During the last few decades bacterial resistance to antibiotics has increased worldwide. As a result the question of a rational use of antibiotics in the treatment of AOM, has become important. Several studies have shown some positive effect of antibiotic treatment in the resolution of AOM, although, in most children, symptoms and MEE resolve spontaneously even without antibiotic treatment (Van Buchem et al. 1981, Kaleida et al. 1991, Burke et al. 1991, Damoiseaux et al. 2000). Two large meta-analyses also showed that antibiotics may improve the relief of symptoms and signs of AOM, but the effect is modest (Rosenfeld et al. 1994, Del Mar et al. 1997). It has been calculated, that 25 children must receive antibiotics to relieve symptoms of AOM in one child in 2-3 days (Rosenfeld and Bluestone 1999). It is also estimated, that seven children should be treated with antibiotics for one

complete clinical resolution of AOM within 7-14 days. Although we know some prognostic factors for AOM (e.g., age<2 years, allergic symptoms, long duration of pretreatment earache, *M. catarrhalis* in MEE) (Jero et al. 1997, Monobe et al. 2003), we still do not have the prognostic tools needed to tell us who will benefit from antibiotic treatment and who will recover spontaneously. In the Netherlands, AOM in children is usually managed with initial observation and only the patients with complications of AOM are treated with antibiotics (Van Zuijlen et al. 2001). In Finland, it is recommended that antibiotic treatment should be started when AOM is diagnosed (Puhakka et al. 1999). If antibiotic treatment is not started, the patient should be examined again after 1-2 days (Puhakka et al. 1999).

In Finland, the recommended first-choice antibiotic for AOM has been either penicillin-V or amoxicillin (Puhakka et al. 1999). In the United States amoxicillin 40mg/kg aday is the drug of choice (Dowell et al. 1999), and doubling the dosage to 80mg/kg aday has proved effective for intermediate non-susceptible *S. pneumoniae* (Seikel et al. 1997). Today in Finland, the incidence of *H. influenzae* and *M. catarrhalis* in MEE of AOM is almost equal to that of *S. pneumoniae* (Kilpi et al. 2001). If antibiotic treatment is started to resolve an infection in the middle ear, the increased number of *H. influenzae* and *M. catarrhalis* positive AOM should also be taken into consideration when the antibiotic is chosen. Because *S. pneumoniae* is the pathogen least likely to resolve spontaneously in AOM (McCracken 1994, McCracken 1999) penicillin or amoxicillin is chosen. In Finland, over 90% of the *M. catarrhalis* and 10-20% of the *H. influenzae* strains produce beta-lactamase and pneumococcal resistance to penicillin is 4% (Kilpi et al. 2001). As a result, in 20-30% of the AOM cases there are penicillin non-susceptible bacteria. If treatment with amoxicillin fails, the recommendation is amoxicillin-clavulanate, or, when the patient is allergic to beta-lactam antibiotics, trimethoprim-sulfa or a macrolide (azithromycin, clarithromycin) is used (Leibovitz et al. 1998, Dowell et al. 1999). In the recent report of Block et al. (2001) treatment with one of the 3rd generation oral cephalosporins, cefdinir or cefpodoxime, was suggested when aminopenicillins failed to cure a middle ear infection. Most bacteriological relapses of AOM occur within 2 weeks after the end of an antibiotic treatment, and AOM that recurs 2 weeks to 1 month after a finished antibiotic treatment is usually a new infection (Leibovitz et al. 2003). This difference should be taken into consideration when an antibiotic treatment is chosen. If the medication cannot be administered orally, a single-dose intramuscular ceftriaxone is a possible treatment alternative (Green and Rothrock 1993, Barnett et al. 1997).

Symptom relieving medication is often used to treat patients with AOM. Analgesics should be used during the first days of AOM to achieve pain relief, but they have no curative effect on middle ear infections (Varsano et al. 1989). Nasal decongestants and antihistamines are widely used to reduce congestion of the mucosa of the eustachian tube and to shorten the

duration of MEE. However, the efficacy of these medications in AOM has not been demonstrated in randomized and placebo-controlled studies (Flynn et al. 2004). The duration of MEE can be even longer with antihistamine treatment than without such a medication (Chonmaitree et al. 2003).

Myringotomy was first introduced in 1802 (Alberti 1974) and has since been used in the treatment of OM. The potential benefits achieved with myringotomy are a relief of earache, a possibility to obtain etiological samples, and a decrease in the number of cases with persisting MEE and RAOM. The randomized trials that have been published concerning the efficacy of myringotomy in the treatment of AOM (Lorentzen and Haugsten 1977, Van Buchem et al. 1981, Van Buchem et al. 1985, Engelhard et al. 1989, Kaleida et al. 1991) have however, not shown statistically significant differences in the clinical outcome of patients receiving and not receiving myringotomy. Therefore, myringotomy is not a routine treatment of AOM and should be reserved for complicated cases (RAOM, ITC and ICC) to identify bacterial etiology of the disease. When a patient has severe otalgia, myringotomy may offer pain relief and thus can be used in selected cases as a symptomatic treatment (Puhakka et al. 1999, Bluestone and Klein 2001).

Tympanostomy tube insertion is widely used in the treatment of RAOM, and it is the most common surgical procedure performed in children in general anesthesia. The idea of using tympanostomy tubes dates back to the 19th century (Alberti 1974), but tubes were reintroduced in the 1950s (Armstrong 1954). Tympanostomy tube insertion is effective in the treatment of RAOM (Gebhart 1981, Gonzalez et al. 1986, Casselbrant et al. 1992). Casselbrandt et al. (1992) randomized 264 children who were between 7 and 35 months of age and who had had recurrent episodes of AOM into three groups: amoxicillin prophylaxis, myringotomy and tube insertion, and placebo. Although there was no difference in the number of AOM episodes between the tympanostomy and placebo groups, the overall time with AOM was 6.6% in the tympanostomy group in a comparison with 15.0% in the placebo group ($P<0.001$). In addition, in the tympanostomy group, the periods with otorrhea were usually otherwise asymptomatic and less troublesome than AOM episodes in the amoxicillin or placebo groups. Tympanostomy tube insertion is considered a safe procedure even in young children (Valtonen et al. 1999). It is recommended as the first choice of operative treatment in cases of RAOM when antimicrobial prophylaxis fails (Bluestone and Klein 2001).

The role of adenoidectomy in the treatment of RAOM has caused wide debate over the years. However, only a few well-designed randomized studies have dealt with this topic. Paradise et al. (1999) found modest, short-term improvement in the outcome of children over 3 years of age with RAOM when adenoidectomy was the first operative treatment. However, among children with RAOM who had been previously treated with tympanostomy tubes, adenoidectomy seems to

reduce the time with AOM and the number of suppurative AOM episodes (Paradise et al. 1990). Mattila et al. (2003) compared the effect of tympanostomy tube insertion alone with tympanostomy tube insertion combined with adenoidectomy among children of 1 to 2 years of age with RAOM. They found no marked difference in the rate of further AOM episodes between the two groups. In a recently published randomised study, the effect of adenoidectomy, chemoprophylaxis, and a placebo were compared as a treatment of RAOM in children less than 2 years of age with no significant differences in the outcome between the groups (Koivunen et al. 2004). Thus, adenoidectomy does not seem to be the primary operative treatment for RAOM, but children with RAOM older than 3 years may benefit from this operation.

2.2 Otitis media with effusion

2.2.1 Definition

OME is defined as a relatively asymptomatic effusion in the middle ear (Bluestone and Klein 2001, Lim et al. 2002). The previously widely used terms serous, secretory, or nonsuppurative otitis media are all included in this definition. The effusion can be serous, mucoid, or even purulent, but, in OME, there are no clinical signs or symptoms of acute infection. This definition gives no time limits for the duration of MEE, but the following classification is recommended: acute (less than 3 weeks), subacute (3 weeks to 3 months), and chronic (longer than 3 months). According to otoscopic findings, tympanometric patterns or hearing thresholds, OME can be classified as mild, moderate or severe (Table 1) (Bluestone and Klein 2001). OME is manifest as a conductive hearing loss in the affected ear. In pneumatic otoscopy the TM is often retracted, and its mobility is impaired. If the TM is translucent, the air-fluid level or bubbles can be seen in the middle ear. However, in OME, opacification of the TM is a frequent finding, and the evaluation of the type of MEE is not always possible by otoscopy.

Table 1. Classification of OME according to otoscopic appearance, tympanometric pattern and hearing thresholds

	Mild	Moderat	Severe
Otoscopy	TM: retracted, mobile, translucent, air-fluid level or bubbles	TM: retracted, immobile, clouded, possible air-fluid level or bubbles	TM: retracted, immobile, completely opaque
Tympanometry	Negative pressure, normal compliance	Low compliance	Low compliance
Hearing threshold	Unilateral disease, better than 20dB in both ears	Bilateral disease, better than 20 dB in the better-hearing ear	Bilateral disease, worse than 20dB in both ears

2.2.2 Epidemiology

OME is, in most cases, a continuum of AOM, and therefore the prevalence and risk factors of OME are closely bound to those of AOM. Teele et al. (1980) showed that, after the first attack of AOM in infants, 10% develop chronic OME (over 3 months). In a small proportion of cases, OME develops spontaneously because of the poor functioning eustachian tube. OME does not produce acute symptoms, and therefore it is difficult to estimate its real prevalence. The reported prevalence rates of OME vary widely and are highly age dependent. The highest prevalence of OME occurs between 6 months and 4 years of age, showing a peak around one year of age (Marchant et al. 1984, Paradise et al. 1997, American Academy of Pediatrics 2004). More than 50% of children suffer from OME during the first year of life. This proportion will rise to over 60% during the second year (Casselbrant et al. 1985, American Academy of Pediatrics 2004). Casselbrant et al. (1985) showed that most OME episodes (80%) resolve spontaneously among preschool children within 2 months. They also showed that the variation in the prevalence of OME was associated with the presence of URI and the season. In a recent study from Turkey, Okur et al. (2004) reported an overall prevalence of 6.5% for children between 6 and 16 years of age. In Finland, Alho et al. (1995) in a birth cohort with a 2-year follow-up reported a 4% prevalence of OME for children less than 2 years of age with the peak incidence occurring between 10 to 16 months of age. A decreasing prevalence of OME with an increasing age has been reported in many studies (Daly 1994, Apostolopoulos et al. 1998, Marchisio et al. 1998).

2.2.3 Pathogenesis

The pathogenesis of OME probably involves most of the same mechanisms as AOM. Although OME often seems to be a continuum of AOM, bacterial growth is found significantly more rarely in the MEE of OME than in that of AOM (Krenke et al. 1988, Giebink 1989). In OME, metaplasia of the middle-ear epithelium with a growing number of mucosal goblet cells leads to the increasing production of mucoid MEE (Ishii et al. 1980, Tos 1980). Mucin production exceeds the mucociliary clearence and causes an accumulation of fluid in the middle-ear cavity. The excessive production and accumulation of fluid in OME is thought to be the result of a residual inflammation after AOM and ineffective pressure control because of tubal dysfunction (Rovers et al. 2004). It has also been proposed that OME and active mucin production in the middle ear could be a natural defensive response of the body against chronic infection, for example, in mucosal biofilm in the middle ear (Ehrlich et al. 2002, Post 2003, Fergie et al. 2004). Many aspects support this assumption. MEE in OME has chemical properties that help to protect against microorganisms. Mucus contains, for example, lysozyme, immunoglobulins, complement components, antimicrobial peptides, cytokines and leukotrienes, all components that can be considered a part of an antimicrobial barrier in the middle ear. Eustachian tube dysfunction can

also be considered merely as a result of an infective process rather than as a mechanical obstruction (de Rue and Grote 2004).

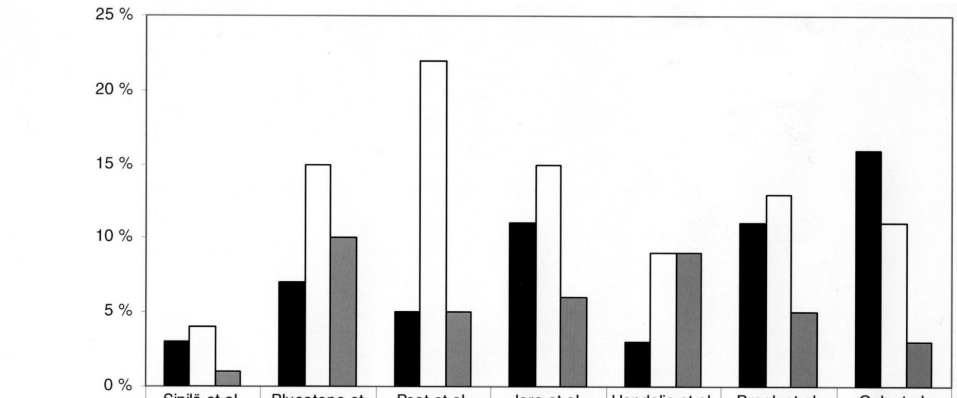
2.2.4 Bacteriology

For a long time OME was considered a sterile condition, and the rare positive bacterial cultures of MEE in OME were considered contamination (Hoople 1950, King 1953). In 1958 Senturia et al. published the results of their study concerning tubotympanitis. They reported bacterial growth in half of the 70 mucopurulent or mucoid middle-ear specimens studied. Since then numerous studies have been carried out on the bacteriology of OME. Liu et al. (1975) studied 100 patients with chronic MEE and found bacterial growth in 52 % of the samples. The three most prevalent organisms found were diphtheroids, *Staphylococcus epidermidis* and *H. influenzae*. They also recognized that the bacterial recovery rate decreased with increasing age. Healy and Teele (1977) examined 57 patients with OME and found bacterial growth in 46% of the obtained MEE specimens. The most frequently found bacteria were *S. epidermidis*, *S. pneumoniae* and *H. influenzae.* In the MEE of the children under 3 years of age the bacterial flora resembled that of AOM. This finding has also been recently confirmed by Brook et al. (2001). Bacteria found from MEE of OME often have an increased resistance to antimicrobial agents. Haddad et al. (2000) found that over half (52.2%) of *S. pneumoniae* isolates identified from the MEE of children with OME were not susceptible to penicillin. Brook et al. (2003) studied 129 children with OME and found bacterial growth in the MEE of 58 patients. In 71% of the specimens, the bacterium cultured was resistant to the used antibiotic. The authors suggest that antibiotic resistant pathogens may have an important role in the persistence of OME.

The results of bacterial cultures in different reports have varied. Figure 2 summarizes the proportions of the most important middle ear pathogens in bacterial cultures of OME in seven selected studies. According to these publications the incidence of bacterial growth in the MEE of OME varies between 21% and 70%. However, negative bacterial cultures have also been reported for OME even with modern culture methods (Saffer et al. 1996). The most frequently found pathogens in OME are the same as found in AOM i.e., *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, with the incidence of 3% to 16%, 4% to 22% and 1% to 10%, respectively. Altogether the three pathogens were found in these selected studies in 8% to 32%. The incidence of *S. aureus* in OME has been from 0% to 10%. *S. pyogenes* is found only occasionally in OME (<1%). *S. epidermidis* and other coagulase-negative staphylococci are the most frequently reported findings concerning OME. They are mostly considered contaminants, although *Staphylococcus epidermidis* has sometimes been proposed as a possible middle ear pathogen (Bernstein et al. 1982, Soriano 1997). Another widely found group of bacteria in OME are diphtheroids or coryneform bacteria. Two of these have been suggested as possible middle-ear pathogens, namely *Turicella otitidis* (Funke et al. 1993, Simonet et al. 1993, Funke

et al. 1994) and *Corynebacterium auris* (Funke et al. 1995). Holzmann et al. (2002) reported that both *T. otitidis* and *Corynebacterium auris* are part of the normal bacterial flora of the external ear canal, and they proposed that these two bacteria are probably not involved in the pathogenesis of OME. However, *T.otitidis* has been cultured in a pure culture of a MEE sample from a patient with acute mastoiditis (AM) (Dana et al. 2001), and therefore the true role of *T. otitidis* in the pathogenesis of OM still remains open. Currently anaerobic bacteria seem to play a minor role in the pathogenesis of OME (Bluestone and Klein 2001).

Figure 2. Comparison of incidences of the three most important middle ear pathogens in bacterial cultures from the MEE of OME in seven selected studies.



	Sipilä et al. 1981	Bluestone et al. 1992	Post et al. 1995	Jero et al. 1996	Hendolin et al. 1999	Brook et al. 2001	Gok et al. 2001
■ S. pneumoniae	3 %	7 %	5 %	11 %	3 %	11 %	16 %
□ H. influenzae	4 %	15 %	22 %	15 %	9 %	13 %	11 %
▩ M. catarrhalis	1 %	10 %	5 %	6 %	9 %	5 %	3 %

Table 2. PCR in the bacteriological diagnosis of OME

Study (n=number of specimens)	Bacterium	PCR positive N(%)	Culture positive N(%)
Hotomi et al. 1993 (n=27)	*H. influenzae*	15(55.6)	0(0)
Post et al. 1995 (n=97)	*S. pneumoniae*	29(29.9)	5(5.2)
	H. influenzae	53(54.6)	21(21.6)
	M.catarrhalis	45(46.4)	5(5.2)
Jero et al. 1996 (n=123)	*S. pneumoniae*	57(46.3)	14(11.4)
Hendolin et al. 1997 (n=25)	*S. pneumoniae*	2(8)	2(8)
	H. influenzae	13(52)	2(8)
	M. catarrhalis	4(16)	4(16)
	A. otitidis	5(20)	0(0)
Hendolin et al. 1999 (n=67)	*S. pneumoniae*	14(20.9)	2(3.0)
	H. influenzae	12(17.9)	6(9.0)
	M. catarrhalis	25(37.3)	6(9.0)
	A. otitidis	31(46.3)	0(0)
Beswick et al. 1999 (n=12)	Universal	12(100)	2(16.7)
Gok et al. 2001 (n=37)	*S. pneumoniae*	8(21.6)	5(13.5)
	H. influenzae	11(29.7)	2(5.4)
	M. catarrhalis	1(2.7)	0(0)

During the last decade, several studies have been carried out to determine whether PCR could be used in the detection of middle ear pathogens in OME. The results of seven selected studies are summarized in Table 2. The main interest in this field of research has been the three clinically most important bacteria, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. However, few studies have been carried out with the intention of more comprehensively settling the question concerning the bacterial load of MEE in OME (Post et al. 1996, Hendolin et al. 1999). The overall rate of PCR-positive effusions from patients with OME has varied

from 46% to 100%. *S. pneumoniae* has been detected in 8% to 46.3% of the MEE samples in cases of OME. The incidence of *H. influenzae* in OME has varied from 17.9% to 55.6%, and, in most studies, it has been the most frequently found OM pathogen. The recovery rate of *M. catarrhalis* has ranged from 2.7% to 46.4% for the MEE of OME. In their study Beswick et al. (1999) used a universal primer targeting all bacteria. Their results differ from those of all other studies. In their material of 12 patients growth occurred in the bacterial culture in only 2 (16.7%) samples, both coagulase-negative staphylococci. However, with PCR all the samples were positive for one to five different bacterial species, which were mostly regarded as opportunists. In all these studies, PCR increased the detection rate of bacteria significantly. PCR proved also to be a specific method for detecting bacterial DNA in MEE.

A. otitidis is a bacterium first found in MEE samples of OME. Faden and Dryja (1989) were the first to report the recovery of a new, possible middle ear pathogen from the MEE of OME. Aguirre and Collins (1992) studied the biochemical properties of this bacterium and, according to a 16S rRNA gene analysis, proposed that it represented a new genus. They named it *Alloiococcus otitis*, but the bacterium was later renamed *Alloiococcus otitidis* (von Graevenitz 1993). It is a fastidious and slowly growing, strictly aerobic gram-positive diplococcus, with special growth requirements (Bosley et al. 1995, Faden and Dryja 1989). It has been cultured in heart-infusion agar plates supplemented with rabbit blood (Bosley et al. 1995, Miller et al. 1996). In bacterial cultures of MEE from OME the recovery rate of *A. otitidis* has been 0% to 5% (Faden and Dryja 1989, Sih et al. 1992, Hendolin et al. 1999). There are no reports of *A. otitidis* in bacterial cultures of AOM. With PCR, *A. otitidis* has been detected in 10% to 50% of the MEE samples of OME (Beswick et al. 1999, Hendolin et al. 1999, Hendolin et al. 2000, Kalcioglu et al. 2002). The presence of *A. otitidis* in a pure culture, and its occasional intracellular location, has raised the question of a possible pathogenic role in OME (Faden and Dryja 1989, Bosley et al. 1995). There are no reports about the possible pathogenic role of *A. otitidis* in other localizations. Durmaz et al. (2002) found *A. otitidis* DNA in nasopharyngeal and external ear canal swabs and proposed that these canals could be the localization sites for *A. otitidis*. Only one report about the antibiotic resistance of *A. otitidis* has been published (Bosley et al. 1995). The *A. otitidis* isolates studied were either susceptible or intermediately resistant to penicillin and ampicillin. All of the isolates were beta-lactamase negative. All strains were resistant to trimethoprime-sulfamethoxazole and, except for one strain, to erythromycin.

2.2.5 Clinical picture and diagnosis

According to the definition of OME, patients with this disease are almost asymptomatic. Chronic MEE is often a consequence of AOM and can be diagnosed during a follow-up. Because of chronic MEE, parents´ suspicion of or patients´ own complaints of hearing loss are common. Occasionally vertigo and tinnitus are encountered. For some children, OME is

diagnosed when a child is examined because of a developmental delay in speech and language. Sometimes difficulties in hearing and communication may lead to behavioral problems. OME can also be found during a routine examination without previously diagnosed AOM and any knowledge of the duration of MEE (Bluestone and Klein 2001).

In the clinical examination pneumatic otoscopy is the primary tool used to diagnose OME. The diagnosis of OME is based on the presence of MEE and the lack of symptoms of acute infection. Pneumatic otoscopy shows the best balance between sensitivity and specificity in the diagnosis of OME. The sensitivity of pneumatic otoscopy is reported to be 94%, and the specificity 80%, for validated observers when the results are compared with those of myringotomy. The true value of pneumatic otoscopy in clinical practice is dependent of the clinicians´ experience in using it and in their ability to evaluate the findings (Pichichero and Poole 2001). Tympanometry and acoustic reflectometry can be used to increase diagnostic accuracy and to confirm the diagnosis of OME (American Academy of Pediatrics 2004).

Audiometric evaluation is recommended in OME when the duration of MEE exceeds 3 months or if there is any suspicion of significant hearing loss or if a delay in speech and language is noted. Hearing testing can be done in primary care for children 4 years of age and older. Children who are under 4 years of age, fail primary care testing, or cannot be tested in primary care should be tested more comprehensively (Joint Committee on Infant Hearing 2000). In reports concerning hearing loss in OME, the pure tone average (PTA) (500, 1000, 2000 Hz) has ranged from 0 to 55 dB (Fria et al. 1985, Kokko 1974). Evidence shows that OME with long duration of MEE and significant hearing loss may have developmental consequences (Friel-Patti and Finitzo 1990, Gravel et al. 1995). However, the recent meta-analysis by Roberts et al. (2004) found only a slight association between OME and the development of speech and language.

OME has a tendency towards significant spontaneous resolution. The resolution of MEE in OME has been studied in many randomized controlled trials (Renvall et al. 1982, Tos et al. 1982, Williamson et al. 1994, Zielhuis et al. 1990). Rosenfeld and Kay (2003) recently published a meta-analysis of studies concerning the natural resolution of AOM and OME. After untreated AOM, the resolution rate was 59% after 1 month and 74% after 3 months. The overall resolution rates for OME of unknown duration were 20% after 3 months and 42% after 6 months. When the duration of chronic OME was unknown, the resolution rate was 26% after 6 months and 33% after 1 year.

2.2.6 Treatment

The tendency of OME towards spontaneous resolution should be kept in mind when treatment is planned. The duration and laterality of MEE and the severity of the symptoms have an influence on the choise of treatment and should be documented at the time of the diagnosis. The clinician should note the children with a risk of speech, language and learning

problems since they may need prompter therapeutic intervention. With otherwise healthy children with no risk factors for developmental disturbances watchful waiting for 3 months from the diagnosis of OME is recommended by the American Academy of Pediatrics (2004).

Medications studied in the treatment of OME have not shown to be effective. Antibiotic treatment of OME has shown short-term benefits, but antibiotics do not offer long-term efficacy (Rosenfeld and Post 1992). Bluestone and Klein (2001) recommend a treatment trial with amoxicillin before surgical intervention for patients who have not been treated with antibiotics and have chronic MEE. When the possible adverse effects and the increase in bacterial resistance are considered, antibiotics should be used in the treatment of OME only in individually chosen cases. The efficacy of both nasal topical and oral corticosteroids for chronic OME has also been studied. Butler and Van Der Voort (2002) conducted a meta-analysis of the studies concerning oral or topical nasal steroids for OME and found a short-term benefit in the resolution of OME, but there was no evidence of a long-term effect. Mandel et al. (2002) came to the same conclusion in their double-blind, randomized study with systemic steroid with or without amoxicillin. They compared the efficacy of 2 and 4 weeks courses of oral prednisolone and amoxicillin together with that of amoxicillin alone for the treatment of chronic OME. After 2 weeks treatment 16.7% and 33.3% of the children were free of MEE in the amoxicillin group and amoxicillin-prednisolone group, respectively. There were no significant differences between the results of 2 and 4 weeks treatment. Within 2 weeks of finishing the treatment, there were no significant differences between the groups. The authors concluded that the medication they used couldn't be universally recommended for the treatment of OME.

The operative treatment of OME has traditionally been tympanostomy tube placement with or without adenoidectomy. Mandel et al. (1989, 1992) carried out two separate trials in which they compared myringotomy with tympanostomy tube placement, myringotomy alone and no surgical treatment in the treatment of chronic OME. They showed that myringotomy with tympanostomy tube insertion resulted in better hearing and less time with effusion than myringotomy alone or no surgery. Later, laser myringotomy was studied in a prospective randomized study in the treatment of OME, but ventilation tube insertion showed to be more effective (Koopman et al. 2004). The role of adenoidectomy in the treatment of OME proved effective in the study of Gates et al. (1987). They randomized 578 children aged 4 to 8 years with chronic OME into four groups. The first received only myringotomy, the second was treated with tympanostomy tube insertion, the third underwent adenoidectomy and the fourth was treated with both adenoidectomy and tympanostomy tube insertion. The mean time with MEE was shorter and the hearing was better in the groups 2, 3 and 4 than in the group 1. Adenoidectomy with myringotomy and adenoidectomy with tympanostomy tube insertion resulted in lowered post-treatment morbidity, and the results between these two

groups were equal. Adenoidectomy is recommended for the operative treatment of OME in selected cases, such as when the size of the adenoids leads to postnasal obstruction or there is suspicion of chronic infection of the adenoids or paranasal sinuses or when, after tympanostomy tube extrusion, chronic MEE recurs (Bluestone and Klein 2001, American Academy of Pediatrics 2004).

2.3 Acute intratemporal and intracranial complications of otitis media

2.3.1 Acute intratemporal complications

The acute intratemporal complications of otitis media include acute mastoiditis, petrositis, labyrinthitis, facial paresis and external otitis (Goldstein et al. 1998).

Acute mastoiditis (AM) is defined as an acute suppurative infection of mastoid gas cell system. It is staged, according to the spread of infection, as follows: AM without periosteitis, AM with periosteitis and acute mastoid osteitis (Bluestone and Klein 2001). An AM without periosteitis is usually an extension of middle ear infection into mastoid. The infection is limited to mastoid mucosa and no classical signs (otalgia, retroauricular pain and swelling, protrusion of the earlobe, fever) of AM are found (Goldstein et al. 1998). In AM with periosteitis the infection spreads to the periosteum and mild signs of mastoid infection are seen. In acute mastoid osteitis, also called coalescent mastoiditis, there is osteitis in the mastoid bone. Mastoid osteitis can spread and lead to abscess formation. When the infection is directed to the lateral wall of the mastoid process, a subperiosteal abscess develops. If the infection spreads to the inferior-medial tip of the mastoid process, a Bezold abscess can develop behind the insertion of sternocleidomastoid muscle. Posterior spread of the abscess leads to the "Citelli abscess". Both Bezold and Citelli abscesses are very rare today (Bluestone and Klein 2001). Mastoiditis is called subacute or latent, when the symptoms and signs of middle ear infection do not resolve within 10-14 days and the clinical signs of mastoiditis are absent (Faye-Lund 1989, Bluestone and Klein 2001). The diagnosis of subacute mastoiditis is made by computed tomography (CT). The spread of infection into the petrosal gas cells is called petrositis. When infection spreads to cochlea or vestibular apparatus the complication is called labyrinthitis. OM or its complications can cause facial paralysis leading to loss of facial function.

Table 3. The incidence of acute mastoiditis and the performed mastoidectomy

Study	Study period	Age, years	Population	Number of mastoiditis cases	Annual incidence of mastoiditis (N/100 000)	Number (%) of mastoidectomies
Palva and Pulkkinen 1959	1954-1959	0-69	400 000[1]	365	18.3	58(16)
Juselius and Kaltiokallio 1972	1956-1971	0-79	160 000[1]	43	1.8	43(100)
Harley et al. 1997	1982-1993	0-15	NS	58	NS	13(22)
Petersen et al. 1998	1977-1996	0-43	600 000[1]	NS	NS	79(NS)
Goldstein et al. 1998	1980-1995	0-17	NS	72	NS	18(25)
Vassbotn et al. 2002	1980-2000	0-41	500 000[1]	61	0.6	50(88)
Butbul-Aviel et al. 2003	1990-2000	0-13	NS	57	NS	5(9)
Katz et al. 2003	1990-2001	0-14	170 000[2]	116	6.1	32(28)

NS= not specified
[1]= Whole population
[2]= Age<14 years

Acute mastoiditis is the most commonly found ITC of OM. The incidences of AM and the number of performed mastoidectomies are summarized in Table 3 for eight selected studies. In the pre-antibiotic era the incidence of AM was high (Lahikainen 1953). Palva and Pulkkinen (1959) studied 12 781 cases of acute and subacute OM during 1954-1959 and found 365 cases of acute or subacute mastoiditis in a population of 400 000 (annual incidence 18.3/100 000). Twenty years later, during 1974-1981, the annual incidence of acute and latent mastoiditis in Finland had decreased to 0.3/100 000 (Palva et al. 1985). The similar decrease in the incidence of AM has been found also in other developed countries. However, recent reports from the United States and Israel show increase in the incidence of AM (Bahadori et al. 2000, Ghaffar et al. 2001, Katz et al. 2003). The incidence of AM has been shown to be associated with the use of antibiotics in the treatment of AOM. Van Zuijlen et al. (2001) compared the incidence of AM in several European countries, Canada, Australia, and the United States. In the Netherlands, where antibiotics are used only in complicated cases of AOM, the incidence of AM in children age 14 years and younger was higher (3.8/100 000) than in countries with liberal antibiotic use (1.2-2.0/100 000) in the treatment of AOM. On the other hand, Antonelli et al. (1999) found increased proportion of resistant bacteria in AM. They suggested that antibiotic-resistant *S. pneumoniae* might be responsible for the increased rate of AM in their study. Therefore the diagnostic accuracy of AOM should be emphasized. A wide use of antibiotics has also been connected to the appearance of subacute or latent mastoiditis with a more chronic clinical picture than that of classical AM (Faye-Lund

1989). The proportion of subperiosteal abscess in children with AM has ranged from 31% to 66% (Petersen et al. 1998, Goldstein et al. 1998).

Otalgia, retroauricular pain and swelling, protrusion of the earlobe and fever are the most frequent clinical signs of AM, especially found in children under 3 years of age (Goldstein et al. 1998, Vassbotn et al. 2002, Katz et al. 2003). A high fever should be considered as a possible sign of complicated AOM with bacteremia (Schutzman et al. 1991). COM and cholesteatoma behind AM are found more frequently in adults than in pediatric patients (Palva and Pulkkinen 1959, Juselius and Kaltiokallio 1972). Most patients have had antibiotic treatment for AOM before the diagnosis of AM, and they usually have had a longer duration of symptoms, too (Luntz et al. 2001). *S. pneumoniae* (25-33%), *H. influenzae* (6-14%), *S. pyogenes* (2-26%) and *Pseudomonas aeruginosa* (6-29%) are the bacteria most frequently found in MEE samples of AM (Harley et al. 1997, Goldstein et al. 1998, Khafif et al. 1998, Katz et al. 2003). *M. catarrhalis*, as a single pathogen, has not been reported to be associated with AM, but Marcinak and Maloney (1987) found *M. catarrhalis* in association with *S. pneumoniae* in ME from a 5-month-old child with recurrent mastoiditis. The use of mastoidectomy in the treatment of AM has varied, but currently the treatment is preferentially conservative. In antimicrobial treatment, 2nd and 3rd generation cephalosporins are preferred (Goldstein et al. 1998, Vassbotn et al. 2002, Katz et al. 2003). Mastoidectomy is usually recommended if coalescent or abscess forming mastoiditis, intracranial complications of AM or cholesteatoma is suspected (Goldstein et al 1998, Taylor and Berkowitz 2004).

Facial paralysis is a frequent complication of AM. Ellefsen and Bonding (1996) reported the annual incidence of facial paralysis to be 5/100 000 in association with AOM. Goldstein et al. (1998) studied 100 children with ITC of OM and found 22 children with a facial paralysis. Fifty percent of the children were 3 years or younger, and 77% were 6 years or younger. The bacteria most frequently cultured from the MEE were *S. pneumoniae* (9.5%) and *P. aeruginosa* (9.5%). Mastoidectomy was performed in 4 (18.2%) children, and 1 patient had facial-nerve decompression. All the children except one achieved a recovery of House grade I (79%) or grade II (16%). For one child the final House grade was V. Mastoidectomy is recommended in facial paralysis if coalescent mastoiditis, chronic suppurative OM or cholesteatoma is involved. Facial decompression is indicated only in cases of total facial paralysis and suspicion of nerve compression (Bluestone and Klein 2001).

Acute petrositis and labyrinthitis are rare complications of AM. Acute petrositis is often associated with an ICC of OM (Goldstein et al. 1998). The signs of petrositis include deep ear pain, discharge from the middle ear, pain behind the eye and paralysis of the abducens nerve. However, the classic Gradenigo´s triad is rarely seen. *S. pneumoniae*, *H. influenzae* and *P. aeruginosa* are the bacteria found in acute petrositis. The treatment for acute petrositis

includes the administration of a intravenous broad-spectrum antibiotic and mastoidectomy (Bluestone and Klein 2001). Labyrinthitis can be classified into serous or toxic, suppurative and meningogenic suppurative labyrinthitis. Serous labyrinthitis is the most common form. However, these infections are so rare that numerical values of the incidence of labyrinthitis in association with AOM or AM in developed countries have not been published recently. The clinical signs of labyrinthitis include sudden mixed hearing loss and vertigo with AOM or its complications. In suppurative labyrinthitis the signs and symptoms are often more profound, and they are often associated with deep ear pain, nausea and vomiting. Goldstein et al. (1998) found 4 patients with labyrinthitis (2 serous and 2 suppurative). They all received broad-spectrum antibiotics intravenously, and in one patient an intact canal-wall mastoidectomy was performed. The patients with serous labyrinthitis recovered fully, but those with suppurative labyrinthitis suffered from profound sensorineural hearing loss in the affected ear.

In conclusion, although acute ITCs of OM are rare today, they still cause morbidity and need prompt treatment. Occasionally permanent damage of the ear leads to hearing loss, vertigo, and sometimes, facial weakness. In children these complications are usually associated with AOM, but in adults COM and cholesteatoma are also significant predisposing factors.

2.3.2 Acute intracranial complications

The acute intracranial complications of OM include meningitis, focal encephalitis, extradural abscess, subdural empyema, brain abscess, sinus thrombosis and otitic hydrocephalus (Bluestone and Klein 2001). In meningitis, the infection has spread to the meninges. The spread of infection can happen either by direct invasion or by hematogenous route. Encephalitis means the spread of infection into brain. An extradural abscess is a collection of purulent material outside, but adjacent to the dura mater. A subdural empyema is a collection of purulent material between the dura mater and the arachnoid membrane. A brain abscess is a collection of purulent material inside the brain. A sinus thrombosis developes usually to the lateral or sigmoid sinus. A mastoid infection produces thrombophlebitis and thrombus formation into the adjacent sinus. Otitic hydrocephalus means increased intracranial pressure without dilatation of the ventricles and abnormalities of the cerebrospinal fluid as a complication of OM. It is usually associated with a lateral sinus thrombosis (Tomkinson et al. 1997).

Acute ICC of OM are encountered today only rarely. In the preantibiotic era, a marked proportion (2.3%) of OM was complicated by ICC (Bluestone and Klein 2001) and led to death in most cases (Kafka 1935). According to the study by Tarkkanen and Kohonen (1970), 99 (3.3/year) and 3 (0.4/year) otogenic brainabscesses were treated in 1930-60 and 1961-1969, respectively in the Otolaryngological Hospital of University of Helsinki. This dramatic decrease in the incidence was considered to be due to the antibiotic treatment of OM and development

Table 4. Proportions of different intracranial complications of otitis media in six selected studies.

Study	Number of patients	Complication N(%)							
		Meningitis	Extradural abscess	Brain abscess	Sinus thrombosis	Otitic hydrocephalus	Encephalitis	Cerebellitis	Death
Juselius and Kaltiokallio 1972, Finland 1956-1971	29	14(48)	8(28)	2(7)	5(17)	0(0)	0(0)	0(0)	0(0)
Samuel et al. 1986, South Africa 1978-1983	224	83(37)	49(22)	53(24)	39(17)	0(0)	0(0)	0(0)	46(21)
Kangsanarak et al. 1995, Thailand 1978-1990	87	43(49)	2(2)	29(33)	20(23)	7(8)	5(6)	1(1)	20(23)
Goldstein et al. 1998, USA 1980-1995	16	2(13)	7(44)	1(6)	6(38)	7(44)	0(0)	0(0)	0(0)
Albers 1999, Netherlands 1993-1996	28	12(43)	0(0)	3(11)	3(11)	2(7)	1(4)	0(0)	1(4)
Sennaroglu and Sozeri 2000, Turkey 1968-1999	41	13(32)	3(7)	41(100)	0(0)	0(0)	0(0)	0(0)	12(29)

of the health care system. A summary of the incidences of different otogenic ICCs is shown in Table 4. Meningitis is found in 13-43% of patients with ICC of OM (Goldstein et al. 1998, Albers 1999, Sennaroglu and Sozeri 2000). Sinus thrombosis and intracranial abscesses are encountered in 0-38% and 0-44% of patients, respectively (Goldstein et al. 1998, Albers 1999, Sennaroglu and Sozeri 2000). Otitic hydrocephalus and encephalitis have been reported in 0-44% and 0-6% of patients, respectively (Goldstein et al. 1998, Albers 1999, Sennaroglu and Sozeri 2000). Mortality from ICCs in conjunction with OM is low in developed countries, but in countries with developing health care systems mortality is still high (23-29%) (Kangsanarak et al. 1995, Sennaroglu and Sozeri 2000).

ICCs arise from the direct invasion of the infection from the middle ear and mastoid or through the hematogenous spread to the intracranial space (Bluestone and Klein 2001). Infection can invade the intracranial space through the progressive thrombophlebitis, by eroding the bony wall of the skull base, or by extending through the pathways like previous skull fractures or perilymphatic fistula (Bluestone and Klein 2001). Meningitis rarely develops through direct invasion (Eavey et al. 1985, Bluestone and Klein 2001). Extradural intracranial abscesses usually develop through the direct invasion when cholesteatoma or osteitis erodes the bony skull base. Subdural empyema generally occurs as a direct invasion, but sometimes through thrombophlebitis. A brain abscess can develop through the hematogenous spreading, but often the underlying cause of infection is cholesteatoma or COM and the infection invades through bony erosion in the tegmen tympani (Sennaroglu and Sozeri 2000). The sigmoid sinus is adjacent to the mastoid, and thrombophlebitis develops through the direct extension to the sinus (Bluestone and Klein 2001). The clinical picture in ICC is often more severe than in other complications of OM. The most common symptoms are headache, fever and drainage of the ear in 49-58%, 25-75%, 8-92% of patients, respectively (Schwaber et al. 1989, Kangsanarak et al.1995, Yen et al. 1995). Earache, nausea, fever and impairment of consciousness are also frequently seen symptoms of ICC. In meningitis, stiffness of the neck is often found. The patients with meningitis, subdural empyema and sinus thrombophlebitis often have signs of septic infection with high fever, seizures, somnolence, neurological deficiencies and severe headache (Yen et al. 1995, Bradley et al. 2002). However, sometimes the symptoms of ICC can be subtle and develop slowly, especially if the underlying OM is treated with antibiotics (Martin-Hirsch et al. 1991). Otitic hydrocephalus is usually accompanied by sinus thrombosis. The pathogenesis of this condition is unknown. It is characterized by increased intracranial pressure without dilated ventricles. The signs and symptoms of otitic hydrocephalus include headache, nausea, vomiting, disturbances in vision, diplopia, abducens paresis, and papiledema (Mathisen and Johnson 1997, Bluestone and Klein 2001).

The bacteriology of otogenic meningitis resembles that of OM with *S. pneumoniae* being

the most commonly grown bacterium in the cultures of cerebrospinal fluid (Juselius and Kaltiokallio 1972, Bluestone and Klein 2001). The bacteriology in intracranial abscesses is far more variable. Both virulent invasive bacteria such as many gram-positive cocci are found, as well as bacteria with low virulence such as many gram-negative bacilli and anaerobic bacteria (Bluestone and Klein 2001). Streptococcus species are found in up to 56% and staphylococcus in 13% of the cultures of intracranial abscess aspirates. Anaerobes are found in 16%, and Enterobacteriaceae appears in 9%. The bacterial etiology of a brain abscess is often polymicrobial (Tattevin et al. 2003). Barry et al. (1999) made a retrospective review of 79 adult patients with otogenic intracranial infection. *S. pneumoniae* was the leading pathogen in 48% of cases. It was found especially in complications with AOM. *Proteus mirabilis* (5%) and anaerobes (7%) were found with cholesteatomatous otitis. *S.aureus* (1%) and *P. aeruginosa* (1%) were found with COM and cholesteatoma.

The diagnosis of an ICC is based on the clinical picture combined with the results of radiological imaging. Computed tomography (CT) of the brain is usually recommended as the primary radiological examination for evaluating otogenic ICC. CT gives more precise information of the bony structures of the mastoid and middle ear and of the invasion of the infection. Magnetic resonance imaging (MRI) can be used to further evaluate ICC because of its higher sensitivity to detect extra-axial fluid collections and possible vascular problems (Vazquez et al. 2003). The treatment of ICC is based on the intravenous administration of broad-spectrum antibiotics (e.g. ampicillin and metronidazole with 3rd generation cephalosporines) and surgery (Mathisen and Johnson 1997, Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy 2000). Mastoidectomy is used to drain the source of infection. Neurosurgical approaches are used to drain the intracranial abscesses. The treatment of brain abscesses usually includes long-term antibiotic treatment and needle aspiration of the abscess (Mathisen and Johnson 1997). Open craniotomy is used rarely. Early operative treatment is crucial, and therefore the need for early and accurate diagnosis should be emphasized. In the treatment of otogenic sinus thrombosis, intravenously administered antibiotics and mastoidectomy are the cornerstones. A recent report (Agarwal et al. 2003) showed that sigmoid sinus thrombosis has a natural capability to recanalize, and, on the other hand, there is no clear evidence of the benefits of anticoagulation (Bradley et al. 2003). Therefore, anticoagulation should not be used as a standard treatment of sigmoid sinus thrombosis (Bradley et al. 2002, Agarwal et al. 2003).

3. AIMS OF THE STUDY

This study had the following two main aims: first, to evaluate the bacteriology of AOM and OME with a special interest focused on *A. otitidis* and its association with these diseases and second, to assess the current incidence and clinical picture of acute complications of OM in southern Finland.

The following special issues were examined:

1. Is *A. otitidis* found in AOM, and is it associated with the clinical outcome of patients with AOM?

2. Is *A. otitidis* associated with the development of OME?

3. Has the clinical picture and outcome of OM patients with ITC and ICC changed during the last 10 years?

4. Which clinical parameters are associated with a poor outcome in ITC and ICC of OM, and can these parameters be used as predictive factors when treatment is planned?

4. MATERIAL AND METHODS

4.1. Patients

The conclusion of the patients included in this study (I, II, III, IV, V) is in Table 5.

Table 5. The patients included in the study

Study	Diagnosis	Age	Number of patients
I	AOM	0-7 years	118
II	OME	0-12 years	123
III and V	ITC or ICC	0-15 years	33
IV	ITC or ICC	>15 years	30

4.1.1 Acute otitis media (I)

Altogether 118 children with 118 episodes of AOM were included in this study. The children were examined either at the Department of Otorhinolaryngology in the Helsinki University Central Hospital (HUCH) or at a private otolaryngological center, in 1990-1992. The guidelines of the Finnish Consensus Conference were followed in the diagnosis and treatment of AOM (Karma et al. 1987). The diagnostic criteria of AOM included both acute ear-related symptoms (at least one of the following: earache, tugging or rubbing of the ear, irritability, restless sleep, fever, loss of appetite, other simultaneous respiratory tract infection) and signs of MEE. The presence of MEE was verified both by pneumatic otoscopy and tympanometry. Children with written informed consent from their parents were included in the study. Children with OME, tympanostomy tubes, spontaneous perforation of the tympanic membrane, or antibiotic treatment within the preceding week were excluded.

4.1.2 Otitis media with effusion (II)

The study population consisted of 123 children with OME, who were referred to the Department of Otolaryngology in HUCH for tympanostomy tube insertion in 1993-1994. The age of the children ranged from 7 months to 12 years (median 2 years 5 months). The inclusion criteria were MEE behind an intact tympanic

membrane for at least 1 month with neither signs nor symptoms of AOM or URI. The onset and duration of MEE was determined from the clinical follow-up data. The presence of MEE was verified both by pneumatic otoscopy and tympanometry. Children with purulent MEE were excluded.

4.1.3 Complications of otitis media (III, IV, V)

All the adult (older than 15 years) and pediatric (15 years and younger) patients treated for acute ITC or ICC of OM during 1990-2000 at the Department of Otorhinolaryngology in HUCH were included. The hospital discharge codes [according to the International Classification of Diseases (ICD-9 and ICD-10)] have been saved in a computer database since April 1990, and this database was used to identify the patients for this study. The inclusion diagnoses of otogenic ITCs included acute and latent mastoiditis, labyrinthitis, acute petrositis and facial paralysis. The diagnostic criteria for AM were a clinical picture of AM presenting with at least one of the following symptoms or signs: postauricular tenderness, erythema, swelling, fluctuation of the mastoid area or protrusion of the auricule in combination with radiological evidence of mastoid infection (effusion in the mastoid with signs of septal destruction) (Rosenfeld and Bluestone 1999) in an OM patient. The otogenic ICC included meningitis, extradural abscess, brain abscess, subdural abscess, intracranial sinus thrombosis and hydrocephalus. In study III the patients with earlier known COM or cholesteatoma were excluded.

4.2 Samples

4.2.1 Acute otitis media (I)

MEE samples were obtained during the initial visit. The ear canal was first mechanically cleaned and the TM anesthetized with 90% liquefied phenol. Myringotomy was performed through the anteroinferior part of the TM. MEE was aspirated into a glass suction tip. A cotton-tipped swab was dipped directly into the aspirate. The swabs were immediately placed in modified Stuart transport media (Transpocult, Orion Diagnostica, Espoo, Finland) and transported at +4°C to the bacteriological laboratory. Thereafter, the sample was rinsed into a polypropylene microtube with 0.5 ml of phosphate buffered saline (PBS). Initially only a bacterial culture was done. Then the rest of the samples were stored at -70ºC for a later PCR analysis.

4.2.2 Otitis media with effusion (II)

All the patients with OME were under general anesthesia during the tympanostomy tube insertion when the MEE samples were obtained. The operation was carried out under the control of an operating microscope without the ear canal being sterilized. In bilateral cases, only the MEE of the right ear was collected. The ear canal was first cleaned and myringotomy was performed in the anteroinferior part of the tympanic membrane. A MEE sample was aspirated with an electric suction device into a Tym-Tap collector (Juhn Tym-Tap®, Xomed Inc., Jacksonville, Florida, USA). The samples were cultured and stored in the same manner

as the samples in study I. MEE was classified as mucoid, mucoserous or serous according to its physical appearance. Clear, glue-like MEE was classified as mucoid. Viscous, but liquid MEE, was considered mucoserous. Clear, running MEE was rated as serous.

4.3 Methods

4.3.1 Clinical evaluation

4.3.1.1 Acute otitis media (I)

The patients' medical history and the signs and symptoms were recorded. The clinical infection status was assessed at the primary visit as mild or strong. The clinical criteria used were the overall clinical condition (good, intermediate, poor), the strength of the ear-related symptoms (e.g. earache, irritability), bilaterality, and the severity of the inflammatory signs of the tympanic membrane (color, position, mobility, disappearance of normal tympanic membrane landmarks). The same ear-, nose- and throat specialist did the clinical assessment in all children. All of the children were treated with amoxicillin clavulanate for 7 days (40 mg of amoxicillin/kg for 24 h, divided into 2 doses). The clinical outcome was evaluated in control visits 2 weeks and 6 weeks later, and at 4-week intervals if clinically necessary. The last control for all the children took place after 6 months. The children whose signs and symptoms of AOM had resolved or had improved by the time of the 2-week control visit were considered cured or improved, respectively. Those whose signs and symptoms had not improved or had worsened during the 2 weeks preceding the control visit were diagnosed as clinical failures. The children whose signs and symptoms first improved but again worsened or recurred between the 2- and 6-week controls were classified as early recurrences. The persistence of MEE over a month after the treatment and the development of asymptomatic MEE of at least 8 weeks´ duration during the 6 months of follow-up were also registered.

4.3.1.2 Otitis media with effusion (II)

The medical history, signs and symptoms of OME were recorded. The diagnostic criteria for OME were MEE of at least one month behind an intact TM and no signs or symptoms of neither AOM nor URI. The presence of MEE was verified both by pneumatic otoscopy and tympanometry (HandTymp 2002, Rexton Danplex A/S, Copenhagen, Denmark). A flat tympanogram with low compliance was considered to indicate MEE. The duration of OME was assessed in each case from the clinical follow-up data. The follow-up was carried out at the Department of Otorhinolaryngology in HUCH. The history of earlier attacks of respiratory infections and AOM within the preceding 6 months was also recorded.

4.3.1.3 Complications of otitis media (III, IV, V)

The patients history of known risk factors for AOM, demographics, previous development and treatment of OM before the admittance to the hospital and possible residual symptoms and consequences after treatment were evaluated

with the use of a structural questionnaire (appendix) sent to each patient. The patients´ clinical data were recorded structurally in a retrospective chart review. The incidence was defined as the number of patients in the age group with a discharge diagnosis of ICC or ITC divided by the number of the population in the same age range in the hospital district (288 000 children, 1 040 000 adults) and the duration of the study period (10 years).

4.3.2 Bacterial culture (I, II)

Cultures were done within 12 hours onto blood agar and chocolate plates and selective blood agar plates with 5 µg/ml of gentamycin. The plates were incubated at +37°C in 5% carbon dioxide for 1 to 3 days. The bacterial identification was done using standard methods (Balows et al. 1991, Virolainen et al. 1994).

4.3.3 Multiplex polymerase chain reaction (I, II)

Multiplex PCR was used for the detection of four middle ear pathogens, including an internal amplification control (Hendolin et al. 2000). DNA purification was based on the QIAamp (Qiagen, Hilden, Germany) kit. The reaction contained specific forward primers for *A. otitidis*, *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, and a universal reverse primer that was labeled with the fluorescent dye Cy5. All of the reactions were prepared from pre-aliquot reagents in a laminar flow hood using aerosol-resistant micropipette tips. Each PCR analysis of 20 to 30 samples included one positive control and two or more blanks with reagents only. After the PCR, the amplification products were detected on an automated Alf Express DNA-sequencer (Pharmacia Biotech, Uppsala, Sweden) (Hendolin et al. 1999). The optimal sample volume in the PCR was investigated with different volumes of eight specimens. From a completed reaction, 5 µl was loaded on the ALF Express sequencing machine. Most of the positive results were obtained with a 20-µl sample, and therefore this volume was chosen for the analysis of the entire set of MEE specimens.

4.4 Statistical methods

In studies I and II, statistical analyses were carried out using the chi-square test with Yates´ correction and the two-tailed Fisher's exact test when appropriate at a significance level of $P<0.05$. McNemar´s test was used when the bacterial detection methods were compared.

In studies III and IV the statistical analysis was carried out with the chi-square test and Fisher´s exact test using a significance level of $P<0.05$ to determine the risk factors and clinical features associated with the performed mastoidectomy, hospitalization for longer than 7 days and permanent complications after treatment.

4.5 Ethics

The study protocol was approved by the Ethics Committee of the Department of Otorhinolaryngology, Helsinki University Central Hospital, Helsinki, Finland.

5. RESULTS AND DISCUSSION

5.1 Methodological aspects

The sample collection in the AOM and OME studies were carried out in 1990-1992 and 1993-1994, respectively. The bacterial culture was done immediately after the sample collection, and the bacterial analysis was carried out using generally accepted methods. Thereafter the MEE samples were stored frozen at -70ºC. The development of multiplex PCR technique (Hendolin et al. 1997) offered a new method to study the MEE samples. The sensitivity of the multiplex PCR for the four bacteria in the OME study was good. In the AOM study the sensitivity for *S.pneumoniae* and especially for *H. influenzae* was markedly lower. In AOM, the proportions of multiplex PCR positive findings were similar to those of the bacterial culture. However, for each bacterial species, there were MEE samples that were positive only by either of the test methods, and negative for the other. Multiplex PCR was the least sensitive for *H. influenzae* (I, Table 3). The DNA purification method may have influenced to the recovery rate of bacterial DNA (Hendolin et al. 2000). The recovery rate of *H. influenzae* DNA has been markedly lower with QIAamp DNA purification than with phenol-extraction (Hotomi et al. 1993, Post et al. 1995, Hendolin et al. 2000). However, the possible effects of the long storage time on MEE samples are not known. The specificity of the multiplex PCR for the four pathogens had been determined in an earlier study by Hendolin et al. (1997). The specificity was later confirmed with various bacterial species found in the nasopharynx. Three of the six viridans group streptococci that were tested, *Streptococcus oralis*, *Streptococcus mitis*, *Streptococcus sanguis*, and two of the three milleri group streptococci, *Streptococcus constellatus* and *Streptococcus intermedius*, yielded an amplification product that was similar to that of *S. pneumoniae*. However, no amplification product was obtained from streptococci that are reported to cause infections of the pharynx and lower respiratory tract (i.e., *Streptococcus agalactiae* (Lancefield group B), *Streptococcus* group C, *Streptococcus* group G). Although the amplification of certain species might lead to false positive results, they have very seldom, if ever, been encountered in AOM or OME (Bluestone et al. 1992, Virolainen et al. 1994, Kilpi et al. 2001). Moreover, the samples in this study were obtained through a myringotomized tympanic membrane, and this procedure minimizes the risk of cross-contamination with the aforementioned reacting species from the nasopharynx.

The studies concerning ITCs and ICCs of OM were carried out using a retrospective chart review and a patient questionnaire. All the clinical records were available and the questionnaire was sent to all of the patients. The patients´ responses to the questionnaire were confirmed with a call when needed. For the children, the response to the questionnaire was 89% (29/33). In the adult group, 20 patients (67%) responded, 3 (10%) patients had died,

and 7 (23%) either refused to answer or could not be found. The author collected the data structurally. All the patients who did not respond to the questionnaire had ITC of OM. There were no other significant differences in the risk factors for AOM, clinical picture, treatment or outcome between those who responded and those who did not respond to the questionnaire.

5.2 Alloiococcus otitidis in acute otitis media (I)

A. otitidis was not found by culture in this study of AOM. Sixty (51%) of the 118 MEE specimens showed growth of any bacteria by culture, and *S. pneumoniae* was the most common finding. The number of culture positive MEE samples was low when compared with 67-84% in other studies (Luotonen et al. 1981, Bluestone et al. 1992). PCR was used to assess the presence of *A. otitidis* in the specimens. There is still some question about the clinical significance of positive PCR results for OM because PCR detects DNA from both viable and non-viable bacteria (Post et al. 1995, Palmu et al. 2004). However, according to the *chinchilla* model of OM, bacterial DNA from non-viable bacteria does not persist longer than a day in an amplifiable form in the presence of an effusion in the middle ear (Aul et al. 1998). Palmu et al. (2004) showed, that a positive pneumococcal PCR seems to indicate the presence of viable, but often nonculturable, *S. pneumoniae* in MEE of AOM. Thus a positive PCR for MEE should be considered as evidence of either bacterial colonization or even ongoing bacterial infection in the middle ear.

A. otitidis was detected in 25% (30 of 118) of the MEE samples of AOM with PCR. It was more often positive in the MEE samples of the older children (>2 years) than in those of the younger children (<2 years), 37% (22 of 59) and 14% (8 of 59), respectively ($P<0.01$) (I, Table 2). There are no other reports of *A. otitidis* in AOM to compare with our results. However, *A. otitidis* has been found in 4,8% of the nasal and ear canal specimens (50 nasal, 95 ear canal) from 50 healthy children by PCR (Durmaz et al. 2002). In this study, no difference was found in the clinical response between the children with *A. otitidis* positive or negative PCR (I, Figure 1). The positive *A. otitidis* PCR finding was not statistically significantly associated with the severity of the infection, the duration of pre-treatment earache, the laterality of the disease or otitis proneness (3 episodes of AOM within 6 months). Nor did the history of respiratory or skin allergy or earlier adenoidectomy differ between the *A. otitidis* positive and the *A. otitidis* negative children.

5.3 Alloiococcus otitidis in otitis media with effusion (II)

Bacteria were cultured in 55 (45%) of the 123 MEE samples of OME. In their recent study, Brook et al. (2003) reported similar finding. In this study, the major OM pathogens (*S. pneumoniae, H. influenzae, M. catarrhalis*) were found in 33% (40/123) of the MEE samples, which is concordant with the results of Bluestone et al. (1992). *A. otitidis* was not detected by culture in this study. However, it has been cultured in 5% of MEE of OME in earlier studies (Faden and Dryja 1989, Bosley

et al. 1995).

Altogether 110 (89%) of the 123 MEE samples were positive in either PCR or culture for one or more of the four studied bacteria. The proportion of PCR-positive specimens was high, but within the same range as in previous reports (Post et al. 1995, Beswick et al. 1999, Hendolin et al. 1999). Twenty-five (20%) of the samples were positive for *A. otitidis* in the PCR. In earlier studies, *A. otitidis* has been found by PCR in 20% to 50% of the MEE samples from children with OME (Hendolin et al. 1997, Hendolin et al. 1999, Kalcioglu et al. 2002). In this study, the detection rate for *S. pneumoniae* (35%) by PCR was a little higher than in earlier studies (Post et al. 1995, Hendolin et al. 1999, Gok et al. 2002). *H. influenzae* was detected in 33% of the MEE samples, which is in the same range as in the study of Gok et al. (2002), but lower than the 52-54.6% found in earlier studies (Post et al. 1995, Hendolin et al. 1997). The number of MEE samples positive for *M. catarrhalis* was higher than reported in other studies (Post et al. 1995, Hendolin et al. 1999, Gok et al. 2001).

A. otitidis was detected more often in the multiple positive specimens than in the single positive specimens ($P<0.05$). The relative frequency of *M. catarrhalis* was greater for the single positive specimens than for the multiple positive specimens ($P<0.05$). The distributions of *S. pneumoniae* or *H. influenzae* between the single and multiple positive MEE samples showed no statistically significant difference (II, Table 1). PCR was significantly more sensitive than culture ($P<0.01$). All but two (5%) of the culture-positive (*H. influenzae*) specimens tested specifically positive in the PCR. *A. otitidis* DNA was detected in 3 (17%) of 18 *H. influenzae* culture-positive MEE samples, 3 (21%) of 14 *S. pneumoniae* culture-positive MEE samples, but none of the 8 MEE samples that tested positive for *M. catarrhalis* by culture. Of the 68 MEE samples negative for any bacteria in culture, 13 (19%) were PCR-positive for *A. otitidis*.

Children aged 2 years or older seemed to have more positive results for *A. otitidis* in the PCR than the younger children did, 19 (24%) of 78 children and 6 (13%) of 45 children, respectively. Hendolin et al. (1999) studied 67 MEE samples from children with OME by multiplex PCR. In their study, 33% of the children younger than 2 years were *A.otitidis* positive compared with 49% of the children 2 years or older. In this study, *S. pneumoniae* occurred in 21 (47%) MEE samples from children younger than 2 years and in 22 (28%) MEE samples from children aged 2 years or older ($P<0.05$). The PCR prevalence of *H. influenzae* and *M. catarrhalis* did not vary in the different age groups. The persistence of MEE differed from 1 to 12 (median 3.5) months, and in 70% of the cases MEE persisted for 3 months or longer. *A. otitidis* was PCR positive in 3 samples (8%) of the MEE that had persisted less than 3 months and in 22 samples (26%) that had persisted 3 months or longer ($P<0.05$). This differs from the results of Hendolin et al. (1999). Their material showed no differences in the proportion of *A. otitidis* in MEEs of different durations. In this study, no statistically significant differences were found

for the findings of the other tested bacterial species in association with the persistence of MEE. Major pathogens were cultured more often in children with recurrent (4) attacks of AOM than in those whose attacks were only occasional (0-3) (49% and 24%, respectively) ($p<0.01$). However, the number of earlier AOM attacks did not statistically significantly correlate with the number of positive effusions in the PCR (II, Table 4). The type of MEE was mucoid, mucoserous or serous in 63 (51%), 56 (46%) and 4 (3%) samples, respectively. Pathogens were cultured in 24 (44%) of the mucoid MEE samples and in 30 (55%) of the mucoserous MEE samples. No pathogens were found in the serous MEE samples by culture only. The proportion of *A. otitidis* was higher in the mucous MEE samples than in the mucoserous MEE samples ($P<0.05$). The proportion of *M. catarrhalis* in the PCR was significantly lower in the mucous MEE samples than in the mucoserous and serous samples ($P<0.05$). For the other bacterial species, no similar associations were observed (II, Table 2). In the study of Hendolin et al. (1999) the proportions of *A. otitidis* and the three major middle-ear pathogens in different type of effusions were equal (1999).

5.4 Acute complications of otitis media in children (III, V)

During the 10-year study period, 33 children [70% (23/33) males and 30% (10/33) females] aged from 3 months to 14.2 years (mean 4.5 years) were treated. The annual age adjusted incidence of all complications was 1.1/100 000. It has slightly decreased over the last three decades (Palva et al. 1985). It is also less than in previous reports from other European countries (Petersen et al. 1998,Vassbotn et al. 2002). In the Netherlands, where the policy is different and the antibiotic prescription rate for AOM is nowadays low, the incidence of acute mastoiditis (3.8/100 000) is markedly higher than that of this study (Van Zuijlen et al. 2001). Forty-two percent (14/33) of the complications occurred in 1990-1994 and 58% (19/33) took place in 1996-2000 (III, Figure 2). The monthly frequency of complications was greatest in autumn ($P<0.05$). Five children (15%) had chronic disease or genetic or developmental disturbances, and 13 (39%) had recurrent URI combined with AOM. The duration of ear symptoms before admission to the hospital ranged from 1 to 45 days (mean 8.03 days), and 70% (23/33) of the patients were admitted to the hospital within 1 week of the occurrence of ear symptoms. All of the children were admitted to the hospital within 2 days after the first signs of complications. The duration of ear symptoms was not statistically significantly associated with the performed mastoidectomy or with the duration of hospitalization.

The most often found signs of complication in children were retroauricular tenderness 28 (85%), erythema 26 (79%) and swelling 24 (73%, III, Table 1) as in many previous studies (Tarantino et al. 2002, Butbul-Aviel et al. 2003). ITC was found in 97% (32/33) and ICC in 3% (1/33) of the patients. The only ICC was an extradural abscess with meningitis. Most of the children (19/33) had strong local or general signs of infection. In addition 6% (2/33) had signs of septic infection with a high fever and

changes in their hemodynamics and level of consciousness. The severity of the signs and symptoms of infection at the time of admittance was not statistically significantly associated with the performed mastoidectomy or hospitalization for over 7 days; similar findings have also been reported in earlier studies (Goldstein et al. 1998, Khafif et al. 1998). Eighteen patients (55%) were on antibiotic medication because of AOM prior to the diagnosis of the complication. Antibiotic treatment or the lack of it before the diagnosis of the complication was not statistically significantly associated with the length of hospitalization or the performed mastoidectomy. Goldstein et al. (1998) studied 100 children with ITC. They found no significant association of antecedent otologic history, presenting symptoms and prior antibiotic use with the need for mastoidectomy or with hospitalization over 7 days. In this study, the signs of subperiosteal abscess, facial paresis or ICC were associated with the performed mastoidectomy ($P<0.05$) and this is concordant with the results of Goldstein et al. (1998).

In the laboratory examinations neither a high level of C-reactive protein (CRP) (>100mg/ml) nor an elevated white blood cell count (>15 000/ mm^3) was statistically significantly associated with the performed mastoidectomy or hospitalization for over 7 days. This agrees with the earlier report by Goldstein et al (1998).

S. pneumoniae, in 25% (8/32) of the MEE or ME samples, was the most frequently found bacteria as in most studies concerning acute complications of AOM (Petersen et al. 1998, Tarantino et al. 2002, Vassbotn et al. 2002). *P. aeruginosa* was cultured in 22% (7/32) of the MEE or ME samples (III, Table 2). The same high incidence of *P. aeruginosa* has been reported also in two reports from Israel (Khafif et al. 1998, Butbul-Aviel et al. 2003). Three of the four children with tympanostomy tubes at the time of the complication showed *P. aeruginosa* in the culture. *M. catarrhalis* grew in the MEE of one child with AM. There are no earlier reports of AM caused solely by *M. catarrhalis*, although one report has shown that *M. catarrhalis* and *S. pneumoniae* together have caused AM (Marcinak and Maloney 1987). Mastoidectomy was performed on both *S. pyogenes* positive patients. No correlation between the performed mastoidectomy and the bacterial species cultured in the MEE was seen among the other patients. All the children underwent a radiographic evaluation. Twentynine (88%) had plain mastoid radiographs, and four (12%) had CT scans. The radioglogical examinations suggested mastoiditis in all children.

The duration of hospitalization ranged from 1 to 23 days (mean 6.6 days). The initial antibiotic treatment in the hospital was intravenous cephuroxime in 94% (31/33) of the children. One child was treated with intravenous penicillin-G and one with intravenous clarithromycin. Bluestone and Klein (2001) recommend cephuroxime sodium as an empirical parenteral antimicrobial therapy until results of culture and susceptibility studies are available. Myringotomy without tympanostomy was performed in 27% (9 of 33) of the children. Tympanostomy tubes were inserted in 58% (19

of 33). In four cases, tympanostomy was the only operative treatment. The remaining 15 tympanostomies were combined with mastoidectomy. Mastoidectomy was performed in 55% (18 of 33) of the children, 12 (67%) of them in 1990-1994 and 6 (33%) in 1995-2000 ($P<0.05$) (III, Figure 2). The proportion of operative treatment was high and similar results have been published in Norway and Denmark (Vassbotn et al. 2001, Petersen et al. 1998). However, the proportion of operative treatment has been markedly lower (9-35%) in many recent studies (Goldstein et al. 1998, Tarantino et al. 2002, Butbul-Aviel et al. 2003). In this study, mastoidectomy was performed on all the children with subperiosteal abscess, facial paresis or ICC. Facial decompression was not done for any of the patients with facial paresis.

During the follow-up, at least 45% (15 of 33) of the patients underwent an audiometric evaluation. The audiometric follow-up was done in the study hospital only in the children who had lowered hearing immediately following the treatment of the complication. No child under 4 years of age underwent an audiometric evaluation. The questionnaire did not reveal any hearing problems with younger children, except for the three who still had problems with RAOM and were treated with tympanostomy tubes. The mild and varying conductive hearing loss of these children accompanied the periods of AOM. After 6 months of follow-up, no hearing loss, facial paralysis or other residual symptoms were found in any patient. No recurrent mastoiditis was found. In previous reports, the proportion of permanent hearing loss, facial paresis and death has been 9-65% (Goldstein et al. 1998, Albers 1999).

5.5 Acute complications of otitis media in adults (IV)

During the 10-year study period 30 patients [57%(17/30) males and 43%(13/30) females] aged 16 to 75 years (mean 42.6 years) were treated. The age-adjusted annual incidence was 0.3/ 100 000. There are no recent reports of the incidence of the complications of OM in adults in Finland. During 1956-1971 the incidence was 2.4/100 000 (Juselius and Kaltiokallio 1972). In this study, there was no seasonal variation in the incidence of the complications. Seventy-three percent (22/30) of the complications were intratemporal and 27%(8/30) were intracranial. All the clinical records were available, and 67% (20/30) of the patients responded to the questionnaire.

Nine of the patients (30%) had a chronic disease (IV, Table 1). Six patients (20%) had recurrent AOM, and OME had been diagnosed earlier in one (3%) patient. Two patients (7%) had a history of mastoidectomy in the past because of COM. The duration of ear symptoms before admission to the hospital ranged from 1 to 28 days (mean 6.43 days), and 73% (22/30) of the patients had been admitted to the hospital within a week after the symptoms of complication had appeared. The ear disease behind the acute complication was AOM, COM and COM with cholesteatoma in 70% (21/30), 17% (5/30) and 13% (4/30), respectively. Barry et al. (1999) studied 79 adult patients with otogenic ITC. In their material AOM, COM and COM with cholesteatoma was diagnosed in 41%, 15% and

22%, respectively. In this study, AOM was diagnosed in 60% (18/30) of the patients before the diagnosis of the complication, and these patients were all on antibiotics before the complication. Antibiotic treatment of the AOM patients before the diagnosis of the complication was statistically significantly associated with a lower number of operative treatments (7/18) when compared with no antibiotic treatment before the complication (11/12) ($P<0.05$), the finding agreeing with Van Zuijlen et al. (2001).

The mastoiditis was classified as classical in 80% (24/30) of the cases and in 20% (6/30) it was latent. Faye-Lund (1989) reported 27 cases of acute or latent mastoiditis during 1985-1988 in Norway. Four (15%) of these were classified latent mastoiditis. In this study, in the ITC group mastoiditis was complicated by subperiosteal abscess, labyrinthitis and facial paresis in 14% (3/22), 18% (4/22) and 27% (6/22), respectively. Fifty percent (4/8) of the ICC cases were intracranial abscesses, 38% (3/8) were meningitis, and 12% (1/8) were sigmoid sinus thrombosis. The proportion of complicated mastoiditis and ICC was higher than in previous reports (Kangsanarak et al. 1995, Albers 1999, Osma et al. 2000, Vassbotn et al. 2002). In this study, the ICC cases were more often associated with a prolonged duration of ear symptoms (over 7 days) when compared with the ITC cases, 5 of 8 and 5 of 22, respectively ($P<0.05$). Latent mastoiditis was diagnosed in 63% (5/8) of the ICC patients but only in 5% (1/22) of the ITC patients ($P<0.05$). Holt and Gates (1983) also showed the association of ICC of OM with latent mastoiditis. They reported nine cases of latent mastoiditis with ICC and extradural abscess developed in two of these. In this study, three of the four patients with cholesteatoma had ICC. The duration of ear symptoms was not statistically significantly associated with the performed mastoidectomy or the duration of hospitalization in the ITC group. All except one of the patients with an ICC were operated on. The only patient who was not operated on had meningitis, and she died before the operative treatment was performed.

Retroauricular tenderness was the most often found local sign of complication in both the ITC and ICC groups (IV, Table 2). Seventy-seven percent of the patients (23/30) had only minor general signs of infection, but 10% (3 with ICC) had signs of septic infection with high fever and changes in hemodynamics and the level of consciousness. Adult patients seem to have less local and general signs of infection than children (Harley et al. 1997, Goldstein et al. 1998, Tarantino et al. 2002). In this study, the ICC patients more often had fever than did ITC patients but the difference was not statistically significant. Spontaneous perforations and otorrhea occurred significantly more often with an ITC than with an ICC ($P<0.05$). However, there was no difference between an ITC and an ICC in the frequency of other local signs of OM and mastoiditis. The severity of general signs and symptoms of infection at the time of admittance was not statistically significantly associated with the need for hospitalization for more than 7 days. This is concordant with the results of the studies in children (Goldstein et al. 1998).

The laboratory examination revealed variable levels of CRP and white blood cell counts. Neither a high CRP level (>100mg/ml) nor an elevated white blood cell count (>15 000/mm³) was statistically significantly associated with the type of complication (ITC or ICC), the performed mastoidectomy or hospitalization for more than 7 days. A bacterial culture of the MEE or ME was taken from 93% (24/30 from the middle ear and 4/30 from the mastoid) of the patients. *S. pneumoniae* (5/30) and *S. pyogenes* (5/30) were the bacteria most often cultured, followed by *P. aeruginosa* (4/30) (IV, Table 3). In previous reports, *S. pneumoniae* and *P. aeruginosa* have been the predominant bacteria in ITCs of children (Goldstein et al. 1998,Tarantino et al. 2002), but there is a lack of recent reports concerning adult OM patients with an ITC. All the patients positive for *P. aeruginosa* and *Escherichia coli* had COM, prolonged AOM or cholesteatoma behind the acute exacerbation of the ear disease. Of the bacterial cultures from the MEE or ME of the patients with intracranial abscesses, two grew *E. coli*, one grew *S. pneumoniae* and one showed *M. catarrhalis*. Of the three MEE specimens from the patients with meningitis one grew *S. pneumoniae* and two showed no growth. These findings agree with the results of earlier reports concerning otogenic ICCs (Kangsanarak et al. 1995, Sennaroglu and Sozeri 2000). The cultures and gram staining of the cerebrospinal fluid of these patients were negative. Of the abscess aspirates from the patients with brain abscess, one grew *E. coli*, one grew *Fusobacterium necrophorum* and *Bacteroides ureolyticus*, but two aspirates were negative in culture. *Enterobacterieae* or *Bacteroides* species are often found in otogenic intracranial abscesses (Mathisen and Johnson 1997, Sennaroglu and Sozeri 2000). Barry et al. (1999) have published a report on 79 adult patients with otogenic intracranial infections, and *S. pneumoniae* (48%) was the most frequently found bacterium, followed by anaerobes (7%) and *H. influenzae* (5%). In this study, all the ICC patients were on antibiotic medication before the cerebrospinal fluid or abscess sample was obtained. There were no differences in the bacterial susceptibility to antibiotics according to the type of ear disease behind the complication.

Plain radiography was the only radiographic examination made for the patients with an ITC or an ICC in 45% (10/22) and 13% (1/8) of the cases, respectively. CT was performed in 55% (12/22) of the ITC patients and in 87% (7/8) of the ICC patients. MRI was done in 38% (3/8) of the ICC patients, but none of the ITC patients. At the end of the decade, CT was the primary radiographic examination done for the patients. All radiological examinations suggested mastoiditis. CT identified subperiosteal and intracranial abscesses in 100% (7/7) of the cases, but in three patients the presence of cholesteatoma behind these complications could not be verified. MRI was used to further examine the localization and spread of brain abscess after CT. These results are in concordance with the present opinion of the use of radiological imaging for these complications (Yates et al. 2002, Vazquez et al. 2003).

The duration of hospitalization ranged from 2

to 32 days (mean 8.2 days). Myringotomy without tympanostomy tube insertion was done in 40% (12/30) of the patients. Eight of them were treated with a combination of antibiotic and myringotomy without other operative treatment. In the case of the remaining four patients with myringotomies without tympanostomy tube insertion, mastoidectomy had also been carried out. A tympanostomy tube was inserted in eight of the 30 patients (27%). In two cases the tympanostomy tube insertion was the only operative treatment. The remaining six tympanostomy tube insertions were done together with mastoidectomy. Mastoidectomy was performed in 60% (18/30) of the patients, and four of the operations were accompanied by the evacuation of an intracranial abscess (IV, Figure 1). This is markedly higher proportion than 35% in previous report by Barry et al. (1999) but lower than 88% in the study of Vassbotn et al. (2002). In this study, mastoidectomy was performed on all the patients with a subperiosteal abscess or ICC. All the patients with COM or cholesteatoma underwent an operation. Facial decompression was done in one patient (17%) with facial paresis. Thirty-three percent (6/18) of the operations were performed in 1990-1994 and 67% (12/18) took place in 1995-2000.

An audiometric evaluation was carried out at least once in 83% (25/30) of the patients. Forty-three percent (13/30) had hearing loss [PTA (0.5-2kHz) more than 20 dB] during the 1-year follow-up. The current acute complication of OM induced permanent hearing loss, ranging from 25 dB to total loss in the affected ear (mean PTA 53 dB), in 30% (9/30) of the patients. The hearing loss was conductive, sensorineural or combined in 7% (2/30), 13% (4/30) and 10% (3/30), respectively. The four patients with pure sensorineural hearing loss all had labyrinthitis. In 75% (3/4) of the patients with sensorineural hearing loss, the affected ear became deaf during the follow-up. One patient (3%) had vertigo after 1 year of the onset of the OM complication, but the vertigo was mild and did not affect the patient´s daily living. In previous studies, hearingloss and vestibular dysfunction has been found in 6-17% of patients (Albers 1999, Barry et al. 1999).

Thirteen percent (4/30) of the patients suffered from chronic serous OM after the complication. One of them developed a chronic perforation of the tympanic membrane, and a tympanostomy tube was inserted in the tympanic membrane of the other three. Seven percent (2/30) of the patients needed continuous follow-up after radical mastoid surgery. One of these patients underwent a revision operation because of residual cholesteatoma.

Five of the six patients (83%) with facial paresis recovered completely. The patient who had total facial paralysis at the onset of the complication suffered from House grade III permanent facial paralysis after 1 year of follow-up. Yetiser et al. (2002) studied 24 patients with facial paralysis due to COM and recovery was achieved only in 60%. Ellefsen and Bonding (1996) reported a material of 23 patients with facial paralysis in AOM. They found full recovery in 96% of patients.

Ten percent (3/30) of the patients have died. In

one (3%) the death was a direct consequence of the OM complication (meningitis). In two (7%) the cause of death was not associated with the ear disease. In the study of Albers (1999), one of the 23 patients with ITC or ICC died. In reports dealing with ICCs of OM the mortality has been 4-23% (Kangsanarak et al. 1995, Yen et al. 1995, Osma et al. 2000, Sennaroglu et al. 2000).

6. GENERAL DISCUSSION

6.1 *Alloiococcus otitidis* in AOM and OME (I, II)

The results of this study show that *A. otitidis* exists both in the MEE of AOM and OME. The higher incidence of *A. otitidis* in the MEE of older children is seen both in AOM and OME. The reason for this finding is still unclear. *A. otitidis* may be a harmless commensal in AOM and OME (or the nasopharynx/ear canal), and the higher incidence of *A. otitidis* in older children may be the result of colonization of this organism due to the interaction of children in day care. In OME, the persistence of MEE for 3 months or longer showed a marked increase in the PCR samples positive for *A. otitidis*. In addition, *A. otitidis* was detected significantly more often in mucoid effusions than in mucoserous ones. *A. otitidis* seems to exist more prominently in chronic OME, and this finding suggests the possibility that *A. otitidis* could prolong the middle ear infection and lead to OME. No other reports have been published about the clinical association of *A. otitidis* in OME. Future research is needed to get more profound knowledge of the possible pathogenetic role and mechanisms of *A. otitidis* in OME.

The response to treatment with amoxicillin clavulanate was similar for the *A. otitidis*-positive and the *A. otitidis*-negative children in AOM. *A. otitidis* has been reported to be either susceptible or intermediately resistant to penicillin, ampicillin and 3rd generation cephalosporins (Bosley et al. 1995). Therefore, these results can only be used to evaluate the clinical significance of *A. otitidis* in AOM patients treated with amoxicillin clavulanate. In the future, the clinical significance of *A. otitidis* in AOM needs to be studied prospectively in a larger population

The multiplex PCR analysis of MEE samples from AOM was found to be as sensitive as the culture method, with the exception of the analysis for *H. influenzae*. In previous studies with MEE samples from OME (Hendolin et al. 1999, Hendolin et al. 2000) and in our OME study, the number of the PCR-positive MEEs has been significantly higher when compared with the culture positive MEEs. This divergence could be explained by the difference in the type of effusion being analyzed. The extractability of bacterial DNA from purulent effusion may differ from that of the mucous or serous effusion of OME. In addition, the extraction method differed from that used in previous studies (Hendolin et al. 2000). The DNA extraction was initiated from cotton swabs that had been used for the inoculation of the culture (i.e., the extraction method did not represent a homogeneous processing of the entire sample). This extra step may have caused the premature lysis of bacterial cells, particularly those of the rigid gram-negative *H. influenzae* cells, and the loss of amplifiable *H. influenzae* genomes.

In OME, *A. otitidis* was often associated with *S. pneumoniae* and *H. influenzae* culture-positive samples, but it was not found in the *M. catarrhalis* culture-positive samples. *A. otitidis* was detected by PCR more often in multiple than in single positive specimens, but with *M. catarrhalis* this relation was reversed. In multiple positive MEE, *M. catarrhalis* was significantly more often associated with gram-positive cocci than with *H. influenzae.* These findings indicate possible interactions between the four bacteria studied. *S. pneumoniae* has been shown to have an inhibitory effect on the growth of *H. influenzae* and *M. catarrhalis* in vitro (Pericone et al. 2000). In an in vitro study, *alpha-hemolytic streptococcus* has been shown to inhibit the growth of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* (Tano et al. 1999). On the other hand, beta-lactamase-producing *M. catarrhalis* may protect *S. pneumoniae* from beta-lactam antibiotics (Budhani and Struthers 1998). It is possible that microbial collaboration and bacterial counteractions lead to changes in the bacteriology of MEE over the course of OME. Whether *A. otitidis* participates in these interactions and hinders the growth of *M. catarrhalis* is a question for further research.

6.2 Severe complications of OM (III, IV, V)

The availability of antibiotics decreased the incidence of ITC and ICC in OM significantly in Finland from the 1950s to the 1970s (Palva and Pulkkinen 1959, Palva et al. 1985, Tarkkanen and Kohonen 1970, Juselius and Kaltiokallio 1972), and it has remained low ever since both in adults and in children (0.3/100 000 and 1.1/100 000, respectively in the present study). The incidence is low even when compared with the reported incidences from the other European countries (Petersen et al. 1998, Van Zuijlen et al. 2001, Vassbotn et al. 2002).

Like in earlier reports (Ellefsen and Bonding 1996, Albers 1999, Osma et al. 2000) concerning acute complications of AOM and COM, also in this study, mastoiditis was the most frequently found single ITC followed by facial paralysis and labyrinthitis. All ICCs, except one, were found in adult patients. The overall number of ICCs was low, but the proportion of intracranial abscesses was higher than in previous reports (Kangsanarak et al. 1995, Albers 1999, Osma et al. 2000). The development of ICC was due to the delay in the diagnosis of the complication. This finding reflects the difficulty in recognizing and understanding the signs and symptoms of an ongoing and progressing ear infection especially in adults. Twenty-one of the adult patients had AOM and 18 of them were on antibiotic medication when the complication was diagnosed. Furthermore, almost 20% of the adult patients had a chronic ear disease that was not diagnosed before the complication, and still another 20% had a latent mastoiditis that had been treated with one or more antibiotic courses before the diagnosis of the complication. This finding addresses the importance of the close patient follow-up and the need for an early otological evaluation of patients with prolonged or progressing ear or neurological symptoms suggesting a complicated ear disease.

Retroauricular pain and fever were the clinical signs of mastoiditis seen in most of the patients. In adults, other signs of acute mastoiditis were seen only rarely reflecting the differences in the etiology and clinical picture between adult and pediatric patients with complications of OM. The reports dealing with the symptoms of ITC and ICC of OM are mostly based on the material from pediatric patients (Harley et al. 1997, Goldstein et al. 1998, Vera-Cruz et al. 1999, Tarantino et al. 2002) or from mixed population of adult and pediatric patients (Kangsanarak et al. 1995, Yen et al. 1995, Petersen et al. 1998, Vassbotn et al. 2002). However, the clinical picture, especially the local signs of ITC of OM in adult patients, seems to be milder than in children.

Only 10% (3/30) of the adult patients had signs and symptoms of septic infection, and they all had an ICC leading to operative treatment. Still, in over half of the patients with ICC, the signs of complication were mild and the symptoms progressed over several days or even a few weeks. In the material of 12 patients with ICC of COM, Schwaber et al. (1989) found drainage of the ear and fever in 75% and 25% of the patients, respectively. More over, ear-related signs and symptoms presented an early phase of the developing infection, and neurological alterations, except headache, were late-phase symptoms that prompted the patient to seek for treatment. In previous studies, cholesteatoma has been found in over half of the otogenic ICCs (Yen et al. 1995, Barry et al. 1999); this rate being even higher than in the present series. Therefore, the possibility of ICCs should be remembered, especially when there is a latent onset of symptoms of mastoiditis, signs of septic infection, neurological symptoms or suspicion of cholesteatoma.

Laboratory examinations, like CRP and white blood cell count, can be used in the follow-up of patients, but their diagnostic value is limited. The diagnosis of complications of OM and the related treatment decisions are based on the clinical picture with the support from radiological findings. During the first half of the study period, plain mastoid radiographs were used in most cases, and the operative decisions were based primarily on the clinical picture of the disease. Today CT is the cornerstone of the radiological diagnosis of acute ITC and ICC of OM. In this study, temporal and cranial CT scans (when ICC was suspected) identified both intratemporal and intracranial abscesses, but cholesteatoma behind the complication was often missed. Therefore, radiological findings determine the choice of surgical approach, but they contribute less to the decision to operate or not and to the prediction of potential hazards.

S. pneumoniae was the most frequently cultured bacteria, as in most studies concerning acute complications of OM (Petersen et al. 1998, Tarantino et al. 2002, Vassbotn et al. 2002). *P. aeruginosa* was found often, especially in patients with RAOM or COM. *M. catarrhalis* was found in one child with ITC and in one adult with ICC. The clinical significance of *M. catarrhalis* in AOM has increased markedly over the past two decades, and it seems that it is also capable of provoking serious complications of OM. Despite the fact that the

bacterial culture was negative in 27% (17/63) of all patients and, in addition, two-thirds of the patients who were on antibiotic treatment before the complication had either accurate antibiotic medication or no growth in the culture, the infection still proceeded. This finding points out the fact that the antibiotic treatment of OM alone is sometimes not effective enough, and patients with a prolonged or rapidly progressing ear disease should be treated in a unit with proper diagnostic and otoneurosurgical facilities. Antibiotic resistance in our material was low like in recent reports from the United States and Israel (Bahadori et al. 2000, Katz et al. 2003). However, the bacteria cultured in the MEE or ME of our patients were more resistant to the used antibiotics than the bacteria found in an uncomplicated AOM in Finland (Kilpi et al. 2001). Because of the variation in the bacteriology of complicated OM and the threat of growing antibiotic resistance, the bacterial culture should always be done from MEE or ME in a complicated OM.

Antibiotics form the basis for the treatment of complications of OM, but the indications for operative measures and their timing is a constant subject of discussion in the literature. Myringotomy with or without tympanostomy tube placement is beneficial to ensure the drainage of the middle ear and to harvest a specimen for bacterial culture. In our study, during the last half of the decade the number of mastoidectomies performed in children decreased, although the number of complications slightly increased. This conservative approach to the treatment of complications of OM in pediatric patients is supported by the reports of Goldstein et al. (1998) and Taylor and Berkowitz (2004). On the other hand, most adult patients with acute complications of OM were treated surgically. The time from the presentation of the ear symptoms to the diagnosis of the complication was not significantly associated with the operative treatment. The consequences of treatment delay however can be disastrous. While the progression of infection can be rapid, the patient with a complicated ear disease should be followed closely, and the treatment should be designed according to the patients individual needs. According to the results of our study and earlier studies (Goldstein et al. 1998, Taylor and Berkowitz 2004), operative treatment is suggested for patients with acute complications of OM when there are signs of abscess forming ITC or ICC or when COM or cholesteatoma is behind the acute complication. Mastoiditis without further complications usually responds to more conservative treatment.

In pediatric patients, mastoidectomy but no facial decompression was done to all patients with facial paralysis. However, it seems that most of the pediatric patients with facial paralysis will recover without operative treatment (Elliot et al. 1996). All adult patients with facial paralysis, except one, were treated conservatively, with good recovery. The adult patient with total facial paralysis was operated on but the recovery was incomplete. Ellefsen and Bonding (1996) have shown that recovery is significantly associated with the severity of facial paralysis in AOM, and this finding was

apparent also in the present study. In adults, facial paralysis associated with OM is often accompanied with COM and cholesteatoma (Osma et al. 2000, Yetiser et al. 2002). In our material, only one patient with facial paralysis had COM but none had cholesteatoma. According to recent recommendations (Elliot et al. 1996, Redaelli et al. 2003) otogenic facial paralysis should be treated as conservatively as possible, and mastoidectomy should be performed only when it is necessary to treat OM and its complications or when the facial paralysis is total.

The response to treatment and the recovery of the pediatric patients was good. Goldstein et al. (1998) concluded in their report that ITC often occurs after inadequately treated AOM. In this study, there was no delay in the diagnosis of ITC, which was probably the most important factor explaining the good results. The child with an extradural abscess and meningitis had a 5-day history of AOM, and the signs of septic infection developed in one day. He had an unclassified developmental retardation and problems with speech production, which may have complicated the assessment of the signs and symptoms of AOM and may have led to a delay in the diagnosis and development of ICC. Although untreated intratemporal and intracranial AOM complications are potentially life threatening, with accurate diagnostic procedures and effective treatment started without delay the prognosis is good.

The risk of a complicated middle ear infection is low today, but the danger of complications still remains. In this study, the proportion of the adult patients with hearing loss was significantly higher than in earlier reports (Yen et al. 1995, Barry et al. 1999). Labyrinthitis induced the most confound inner-ear damage, and therefore it was the single most disabling form of ITC. The hearing loss of the patients with labyrinthitis was profound or total in all cases. However, the vertigo associated with labyrinthitis was well compensated in all the patients. Antibiotic treatment has decreased the mortality associated with the complications of OM, but it is still high in countries with a developing health care system (Samuel et al. 1986, Kangsanarak et al. 1995, Sennaroglu and Sozeri 2000). The overall mortality associated with the ITC and ICC of OM in this study (3.3%) was at the same level as described earlier (1.3-5%) (Leopold and Lagoe 1988, Yen et al. 1995, Barry et al. 1999). The mortality associated with ICC (12.5%) was comparable with the 10% reported by Gower and McGuirt (1983). The death of one patient reminds of the potential dangers of OM. Special awareness is needed when a patient with OM complains headache or develops neurological symptoms.

7. SUMMARY AND CONCLUSIONS

This study was carried out to explore the bacteriology and current clinical picture of OM and its complications. Special interest was focused on the incidence and clinical association of *A. otitidis* in AOM and OME and on the incidence and clinical picture of acute complications of OM in children and adults.

Although not culturable, *A. otitidis* was detected by PCR in a marked proportion of the MEE of AOM. The results of this study suggest that, in AOM treated with amoxicillin-clavulanate, *A. otitidis* has no clinical significance, and it does not increase the risk of OME developing after AOM. However, the clinical significance of *A. otitidis* in AOM needs to be studied prospectively in a larger population.

PCR proved to be a sensitive and specific method for detecting *A. otitidis* in MEE of OME. *A. otitidis* was often found in mucoid MEE (20%), and its presence in MEE correlated significantly with the persistence of effusion in the middle ear. This finding suggests that *A. otitidis* could be one of the factors leading to the prolongation of inflammation in the middle ear and the development of OME.

Acute ITC and ICC of OM are rare today, but they still have a hazardous potential even to disable and lead to a lethal outcome. Among children these complications are usually intratemporal and present in conjunction with AOM, but among adults ICCs and COM and cholesteatoma behind the complication should be suspected more easily, even if the patient has not had earlier ear problems. In adults the clinical picture of ITC and ICC of OM is often slowly progressing and mild. However, the signs of septic infection or neurological disturbances strongly suggest ICC. The bacteriology and the bacterial resistance to antibiotics in ITC and ICC differ markedly from those of AOM. Therefore, the bacterial etiology should always be determined in the case of prolonged AOM. Patients with a prolonged middle-ear infection or with neurological symptoms secondary to OM should be evaluated and treated in a unit with otoneurosurgical facilities. Antibiotics are the basis of the therapy. Operative treatment is suggested in abscess forming ITC or ICC of OM or when COM or cholesteatoma is found to be behind these complications. With early diagnosis and accurate treatment, the prognosis of these complications is good.

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Espoo, December 2004
Kimmo Leskinen

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APPENDIX

Välikorvatulehduksen komplikaatiot HYKS:n korva-, nenä- ja kurkkutautien klinikassa 1990-2000

Potilaskysely

Olkaa hyvä ja täyttäkää ensin henkilötieto-osa tutkimuksen myöhemmässä vaiheessa tapahtuvaa tunnistusta varten. Tämän jälkeen seuraa kysymysosa, johon vastaatte laittamalla rastin kyllä, ei tai en osaa sanoa ruutuun kunkin kysymyksen kohdalla. Lopuksi on vielä muutama tarkentava sanallinen kysymys. Omia kommentteja (koskien esim. hoitoa,toipumista tai tätä tutkimusta) varten on varattu tilaa lomakkeen loppuun.

Henkilötiedot:

Nimi: _____ Syntymäaika: _____

Osoite _____

Kysymysosa

Välikorvatulehduksen riskitekijät
(sairastumisen aikoihin)
Kysymyksiin 1.-6. vastataan vain lapsipotilaiden osalta

		ei	kyllä	en osaa sanoa
1.	Tupakointia kotona sisätiloissa?	☐	☐	☐
2.	Onko lasta imetetty? (kesto ____kk)	☐	☐	☐
3.	Onko sisaruksia? (lukumäärä ___)	☐	☐	☐
4.	Päivähoito kotona?	☐	☐	☐
5.	Päiväkodissa?	☐	☐	☐
6.	Perhepäivähoito?	☐	☐	☐
7.	Akuutteja välikorvatulehduksia yli 3/6kk?	☐	☐	☐
8.	Liimakorvatauti ennen komplikaation hoitoa?	☐	☐	☐
9.	Korvan tai kasvojen kehityspoikkeavuuksia?	☐	☐	☐
10.	Kromosomipoikkeavuuksia(esim. Down sdr)?	☐	☐	☐
11.	Huuli- tai suulakihalkio tiedossa?	☐	☐	☐
12.	Immuunipuutostauti tiedossa?	☐	☐	☐

Sukuhistoria

Välikorvatulehduksen komplikaatioilla tarkoitetaan seuraavassa välikorvatulehduksen aiheuttamaa

- korvan seudun tai korvalokeroston märkäpesäkettä
- aivokalvon tulehdusta tai kallon sisäistä märkäpesäkettä
- tasapainoelimen tulehdusta
- kasvohermohalvausta

		ei	kyllä	en osaa sanoa
1.	Vanhemmilla välikorvatulehduksia?	☐	☐	☐
2.	Vanhemmilla välikorvatulehduksen komplikaatioita?	☐	☐	☐
3.	Sisaruksilla välikorvatulehduksia?	☐	☐	☐
4.	Sisaruksilla välikorvatulehduksen komplikaatioita	☐	☐	☐

Lapsen sairaushistoria	ei	kyllä	en osaa sanoa
1. Oliko lapsi/olitteko ennen sairaalaan joutumista ollut perusterve?	☐	☐	☐
2. Onko kroonisia sairauksia tiedossa?	☐	☐	☐
3. Oliko todettu liimakorvatautia ennen välikorvatulehduksen komplikaatiota?	☐	☐	☐
4. Onko liimakorvatautia nykyisin?	☐	☐	☐
5. Oliko kitarisa poistettu ennen komplikaatiota?	☐	☐	☐
6. Oliko tehty tärykalvoputkitusta ennen välikorvatulehduksen komplikaatiota?	☐	☐	☐

Olkaa hyvä ja vastatkaa vielä alla oleviin kysymyksiin sikäli kuin pystytte

Oliko todettu välikorvatulehdus ennen komplikaatiota?

Sairaudet 2 viikkoa ennen komplikaatiota?

Lääkitykset 2 viikkoa ennen komplikaatiota?

Tiedossa olevat krooniset sairaudet?

Sairaudet 3 kk ajalta ennen välikorvatulehduksen komplisoitumista?

Välikorvatulehdusten määrä kokonaisuudessaan ennen komplikaatiota?

Välikorvatulehdusten määrä komplikaatiota edeltäneen 6 kk aikana?

Montako kertaa kaikkiaan tehty kitarisan poisto?

Milloin viimeksi ennen välikorvatulehduksen komplikaatiota tehty kitarisan poisto? _____kk
Montako kertaa kaikkiaan laitettu tärykalvoputket?

Milloin viimeksi ennen välikorvatulehduksen komplikaatiota laitettu tärykalvoputket? _____kk
Onko välikorvatulehduksen komplikaation jälkeen ilmennyt ongelmia kuulossa?

Onko välikorvatulehduksen komplikaation jälkeen ollut haittaavaa huimausta?

Omat kommentit

Kiitos!